Annex 3: Systematic Review Evidence Profiles & Evidence-to-Decision tables

Guidelines for the
Medical Management of Cancer Pain
in Adults and Adolescents

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PICO Questions answered by Systematic Review

Key Question 1: Choice of pharmacotherapy for analgesia

1.1. In adults (including elderly) and adolescents with pain related to active cancer, are there any differences between NSAIDs, paracetamol (acetaminophen), and opioids at the stage of initiation of pain management in order to achieve rapid, effective and safe pain control?

1.2. In adults (including older persons) and adolescents with pain related to active cancer, are there any differences between opioids for maintenance of therapy in order to achieve rapid, effective and safe pain control?

1.3. In adults (including older persons) and adolescents with pain related to active cancer receiving first-line treatment with opioids for background pain, what is the most effective opioid treatment for breakthrough pain?

Key Question 2: Opioid Rotation/Switching

2.1. In adults (including older persons) and adolescents with pain related to active cancer and who are taking a single opioid, what is the evidence for the practice of opioid rotation or opioid switching as compared with continuing use of one opioid in order to maintain effective and safe pain control and minimize adverse effects?

Key Question 3: Opioid Formulation

3.1. In adults (including older persons) and adolescents with pain related to active cancer, what is the evidence for the benefit of administering modified release morphine regularly as compared with immediate release morphine on a 4-hourly or as required basis, in order to maintain effective and safe pain control?

3.2. In adults (including older persons) and adolescents with pain related to active cancer, what is the evidence for the benefit of using the subcutaneous, transdermal, or transmucosal route as compared with the intramuscular and intravenous routes when the oral route for opioids is inappropriate (e.g. adults (including older persons) and adolescents with diminished consciousness, ineffective swallowing or vomiting) in order to maintain effective and safe pain control?

Key Question 4: Opioid Cessation

4.1. In adults (including older persons) and adolescents with cancer-related pain, what is the evidence for certain dosing regimens or interventions in order to effectively and safely cease opioids?

Key Question 5: Adjuvant Treatments

5.1. In adults (including older persons) and adolescents with cancer-related pain are adjuvant steroids more effective than placebo, no steroids, or other steroids to achieve pain control?

5.2. In adults (including older persons) and adolescents with bone metastases, what is the evidence for the use of bisphosphonates or monoclonals compared with each other or no treatment or other bisphosphonates in order to prevent and treat pain

5.3. In adults (including older persons) and adolescents with cancer-related neuropathic pain, what is the evidence for the use of anti-depressants compared with placebo, no anti-depressant or other anti-depressants in order to relieve pain?

5.4. In adults (including older persons) and adolescents with cancer-related neuropathic pain, what is the evidence for the use of second generation anti-epileptics such as gabapentin or first generation anti-epileptics such as carbamezapine or sodium valproate compared with placebo, no anti-epileptic, or other antiepileptics in order to achieve rapid, effective and safe pain control?

Key Question 6: Radiotherapy

6.1. In adults (including older persons) and adolescents with pain related to bone metastases, what is the evidence for the use of low-fractionated radiotherapy as compared with high-fractionated radiotherapy or radioisotopes in order to achieve rapid, effective and safe pain control?

6.2. In adults (including older persons) and adolescents with pain related to bone metastases, what is the evidence for radiotherapy or radioisotopes as compared with no radiotherapy or radioisotopes in order to achieve rapid, effective, and safe pain control?

Key Question 1: Choice of pharmacotherapy for analgesia

1.1. In adults (including elderly) and adolescents with pain related to active cancer, are there any differences between NSAIDs, paracetamol (acetaminophen), and opioids at the stage of initiation of pain management in order to achieve rapid, effective and safe pain control?

Five eligible RCTs evaluated outcomes other than pain relief among people with cancer who were initiating pain management (see Evidence Profile 1.1).[1-5] However, few trials, including these, clearly distinguished between patients at pain management initiation and those on maintenance treatment. The determination of whether all or most patients included in a study were initiating treatment was, in part, a matter of judgment. Nevertheless, the five eligible studies included people with cancer pain who were naïve to strong opioids (or beginning opioid treatment).

The studies evaluated the following medications: Buprenorphine, Fentanyl, Morphine, and Oxycodone. No study listed or reported on respiratory depression among their study participants.

Two trials compared medication classes to evaluate relief of pain, providing very low strength of evidence favoring high potency opioids to relieve pain more frequently than low potency opioids (RR 1.80; 95% CI 1.42, 2.29) and favoring combination low potency opioids + NSAID to relieve pain more frequently than NSAIDs alone (RR 1.36; 95% CI 0.98, 1.87).

One trial compared medication classes to evaluate degree of pain relief, providing very low strength of evidence regarding high potency opioids compared with low potency opioids, suggesting no difference (estimated net difference = -13.3; 95% CI -87, 60 on a scale of 0 to 100 [worst]).

The three studies provided moderate strength of evidence of similar rates of confusion with either morphine or oxycodone (RR = 0.85; 95% CI 0.50, 1.44), nominally favoring morphine. One study compared all four opioids, providing low strength of evidence of similar rates of confusion with all four medications (from 36% to 47%).

Evidence Profile 1.1. Analgesics at Initiation of Pain Management

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Opioids, NSAIDs, or Paracetamol (Acetaminophen)**	**Other Opioids, NSAIDs, or Paracetamol**	**Relative (95% CI)**	**Absolute (95% CI)**		
Pain relief (categorical) (follow-up: 7-28 days)												
2 [1,2]	RCT	serious [A]	N/A	not serious	serious [B]	single study per comparison	Opioid, high potency 83/110 (75%)	Opioid, low potency 49/117 (42%)	1.80 (1.42, 2.29)	**336 fewer per 1000** (from 215 to 456 fewer)	Very Low	CRITICAL
							Opioid, low potency + NSAID 47/83 (57%)	NSAID 33/79 (42%)	1.36 (0.98, 1.87)	**149 fewer per 1000** (from 4 more to 301 fewer)		
Pain relief (continuous) (28 days, assessed with Numerical Rating Scale from: 0 to 100 [worst] [C])												
1 [1]	RCT	serious [A]	N/A	serious [D]	serious [B,E]	single study	Opioid, high potency 110	Opioid, low potency 117	-13 (-87, 60)		Very Low	CRITICAL
Pain reduction maintenance												
0									not estimable		-	CRITICAL
Quality of life												
0									not estimable		-	CRITICAL
Functional outcomes												
0									not estimable		-	IMPORTANT
Adverse events: Respiratory depression												
0									not estimable			IMPORTANT
Adverse events: Confusion (follow up: range 14 days to 1 year)												
3 [3,4,5]	RCT	not serious	not serious	not serious	serious [E]	none	**Morphine CR:** 69/276 (17% [F])	**Oxycodone CR:** 73/282 (21% [F])	**RR 0.85** (0.50, 1.44)	**26 more per 1000** with oxycodone CR (from 75 fewer to 85 more)	Moderate	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Opioids, NSAIDs, or Paracetamol (Acetaminophen)	Other Opioids, NSAIDs, or Paracetamol	Relative (95% CI)	Absolute (95% CI)		
1 [3]	RCT	not serious	N/A	not serious	serious [E]	single study	515 total [G]		**Other Medications [G] All NS [H]**		Low	IMPORTANT

Abbreviations: CI: *confidence interval;* ***CR*** *= controlled release;* ***NS:*** *nonsignificant;* ***NSAID****: Nonsteroidal anti-inflammatory medication;* ***RCT****: randomized controlled trial(s).*

Explanations

A. Lack of blinding.
B. Small studies.
C. Scales transformed to 0 to 100, as necessary.
D. Estimated effect based off of median and range data.
E. Wide confidence intervals.
F. Meta-analyzed value.
G. Buprenorphine, Fentanyl, Morphine CR, Oxycodone CR.
H. All pairwise analyses between the 4 medications listed in footnote C are statistically nonsignificant, with 95% CI ranging from 0.58 to 1.27 across estimates of RR.

Trials

1. Bandieri E, Romero M, Ripamonti CI, et al. Randomized Trial of Low-Dose Morphine Versus Weak Opioids in Moderate Cancer Pain. J Clin Oncol; Feb 2016.
2. Strobel E. Drug therapy in severe tumor pain. Comparative study of a new combination preparation versus diclofenac-Na. Fortschr Med. 1992.
3. Zecca, E., Brunelli, C., Bracchi, P., et al. Comparison of the Tolerability Profile of Controlled-Release Oral Morphine and Oxycodone for Cancer Pain Treatment. An Open-Label Randomized Controlled Trial. J Pain Symptom Manage; Dec 2016.
4. Riley, J., Branford, R., Droney, J., et al. Morphine or oxycodone for cancer-related pain? A randomized, open-label, controlled trial. J Pain Symptom Manage; Feb 2015.
5. Corli, O., Floriani, I., Roberto, A., et al. Are strong opioids equally effective and safe in the treatment of chronic cancer pain? A multicenter randomized phase IV 'real life' trial on the variability of response to opioids. Ann Oncol; Jun 2016.

Evidence-to-Decision table 1.1		
In adults (including older persons) and adolescents with pain related to active cancer, are there any differences between NSAIDs, paracetamol (acetaminophen), and opioids at the stage of initiation of pain management in order to achieve rapid, effective and safe pain control?		
POPULATION:	Adults (including older persons) and adolescents with cancer-related pain	Recent estimates state that 25.5 million people died in 2015 in serious health-related suffering, of which 80% lived in countries that lack access to palliative care and pain relief[6]. Cancer was responsible for 8.8 million deaths in 2015[7]. Expert opinion and data from country experiences from several low-income countries suggest that approximately 80% of people dying from cancer experience moderate or severe pain lasting on average 90 days[6]. A recent systematic review of published evidence reports a similarly high figure that 66.4% of patients with advanced, metastatic, or terminal disease experience pain.[8] **<u>Current recommendations</u>** The current recommendations rely on the 1996 WHO Guidelines on Cancer Pain Relief, which employs the three step analgesic ladder, which recommends 'sequential use of drugs': first a non-opioid with or without an adjuvant; then if pain is not relieved, 'an opioid for mild to moderate pain should be added'; if this combination 'fails to relieve the pain, an opioid for moderate to severe pain should be substituted'. The GDG in 2017 were keen to note that this sequential recommendation was misleading as it implied that pain relief should start with non-opioids and ramp up to strong opioids, when in fact patients may enter at any point of the analgesic ladder. The array of specific non-opioids considered included acetylsalicylic acid (ASA) 500-600mg every 4-6 hours, other NSAIDs (such as those on essential medicines lists, e.g. ibuprofen 400mg every 4-6 hours and indomethacin 25mg every 6 hours), and paracetamol 650-1000mg every 4-6 hours. Specific choice from this selection "will depend on factors such as local availability and cost." The guidelines take note of typical contraindications such as gastric irritation, toxicities, hypersensitivity reactions, and other potential adverse effects of these medications, and notes the maximum dosages for each of the medications to avoid excess adverse effects: maximum 4g
INTERVENTION:	Analgesics (NSAIDS, paracetamol, opioids)	
COMPARISON:	Other analgesics	
MAIN OUTCOMES:	• Pain relief • Pain relief speed • Pain relief maintenance • Quality of life (QoL) • Functional outcomes • Respiratory depression (adverse event) • Confusion (adverse event)	
STRATIFICATIONS:	• Age (adults, elderly, adolescents, children) • History of substance abuse • Refractory pain	
SETTING:	All	
PERSPECTIVE:	Population	

		of ASA per day, maximum 6g paracetamol per day, maximum 3g ibuprofen per day, maximum 200mg indomethacin per day. The 1996 recommendations split opioid analgesics into those used for mild to moderate pain and those used for moderate to severe pain. It recommends opioid analgesics be given by mouth if possible. It notes that there is no standard recommended dose because responses of patients vary, and it recommends that dose takes into account tolerance and the development of physical dependence, as well as that lower starting doses be used in older persons. The guidelines also recommend that the regimen offered accounts for disease-induced alterations in opioid pharmacokinetics, especially in cirrhosis and renal failure. If a patient appears to be intolerant to morphine, an alternative strong opioid is recommended. The 1996 guidelines state that the initial dose of an opioid for moderate to severe pain depends mainly on the patient's previous medication. For those who have previously received 60-100mg of codeine by mouth, they state that a starting dose of 10-15mg of morphine is usually adequate. Dose should be halved if the patient becomes somnolent after the first dose and is free of pain. If after 24 hours on this medication, Not all medications were discussed with regards the initiation of pain management. The recommended regimens for each medication discussed are: • Codeine by mouth 30-120mg every four hours. • Morphine by simple aqueous solution or tablet every four hours, or by slow release tablets every 12 hours. The correct dose is "the dose that works" to relieve a patient's pain. Typical starting dose 10-15mg. • Standardised opium – no specific starting dose given. • Tramadol usual dose by mouth 50-100mg every 4-6 hours. • Hydromorphone usual starting dose 1-2mg by mouth or 1mg by subcutaneous injection, analgesia lasting 3-4 hours. • Methadone 5-10mg by mouth or by subcutaneous injection, analgesia lasting 6-12 hours. • Levorphanol usual starting dose 1-2mg by mouth four times per day. Half dose for injection.

		• Pethidine 50-100mg may be given every three hours as a starting dose, or more frequently in patients with severe cancer pain. • Oxycodone usual starting dose 5-15mg by mouth or rectally, analgesia lasting 3-5 hours. • Buprenorphine dose to account for its 60 times greater potency than orally administered morphine. When pain is no longer controlled by buprenorphine, 100 times the previously administered total daily dose of buprenorphine should be given of oral morphine sulfate in a four hourly regimen instead. The GDG identified the initiation of pain management as a time point of interest. Given the variety of views on the topic outside of the GDG, they decided that evidence should be collected for all relevant medications, i.e. paracetamol, NSAIDs, and opioid analgesics.

	CRITERIA	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** Yes	**Research evidence:** Expert opinion and data from country experiences from several low-income countries suggest that approximately 80% of the millions of people dying from cancer each year experience moderate or severe pain lasting on average 90 days, most of whom lived in countries with inadequate access and availability of adequate pain management[6]. Up to date guidance is needed in order to overcome attitude and knowledge barriers to the delivery of adequate pain management[9]. **Additional considerations:** None.

BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Yes ☐ No ☐ Uncertain ☒ Yes	**FIve randomized controlled trials** compared analgesics used at pain management initiation. All but one trial (that did not report data) included patients with multiple cancer types. All trials were conducted in adults or elderly adults, two of which were restricted to older persons. Six trials compared different opioids, one evaluated the addition of paracetamol, and one compared a NSAID to combination opioid and NSAID. **BENEFITS and HARMS** • Based on **one trial,** we are uncertain whether **high-potency opioid** or **low-potency opioid** better **relieve pain** as the strength of the evidence has been assessed a **very low** (RR 1.80; 95% CI 1.42, 2.29)**.** Based on **one trial,** we are uncertain whether **high-potency opioid + NSAID** or **NSAID alone** better **relieve pain** as the strength of the evidence has been assessed a **very low** (RR 1.36; 95% CI 0.98, 1.87)**.** • Based on **one trial,** we are uncertain whether **high-potency opioid or low-potency opioid reduce pain** more as the strength of the evidence has been assessed a **very low** (Net difference = -13; 95% CI -87, 60 on a 0-100 [worst] scale)**.** • **No trial** reported on **pain relief speed**. • **No trial** reported on **pain relief maintenance**. • **No trial** reported on **QoL**. • **No trial** reported on **functional outcomes**. • **No trial** reported on **respiratory depression.** • **Three trials** reported on confusion. The three trials provided **moderate strength of evidence of similar rates of confusion between morphine controlled release and oxycodone controlled release** (RR = 0.85; 95% CI 0.50, 1.44**).** **One trial** had **low strength of evidence of no differences among buprenorphine or fentanyl also compared to morphine controlled release and oxycodone controlled release.** **STRATIFICATIONS** • Studies conducted in adults with a wide age range, without stratification into adolescent, non-older persons, and older persons. • Studies provide no data regarding history of substance abuse. • Studies provide no data regarading refractory pain. **SUMMARY** We are uncertain about relative pain relief effects of different classes of analgesics. Morphine controlled release and oxycodone controlled release probably result in similar rates of confusion. Buprenorphine and fentanyl may result in similar rates of confusion, also compared to morphine controlled release and oxycodone controlled release. **<u>Additional considerations</u>**

		The GDG were keen to note that this conclusion of uncertainty with regards to the balance of desirable vs undesirable effects for the studied analgesics does not indicate uncertainty about whether to use analgesics or not – the uncertainty pertains to difference *between* different medications, not to their use absolutely.
ACCEPTABILITY & PREFERENCES	**Is there important uncertainty or variability about how much people value the options?** Major variability yes Minor variability Uncertain **Is the option acceptable to key stakeholders?** Yes No Uncertain yes	**<u>Research Evidence:</u>** There is quite a lot of variability across countries, cultures, clinicians, families, and patients with regard to values on the use of opioid medications[10]. The GDG agreed that all options should be acceptable to key stakeholders such as clinicians and policymakers, but ill-founded opiophobia continues to be an issue with acceptability in many settings worldwide[11]. **<u>Additional considerations</u>** The GDG took into account the often contradictory views of overall patient preference for strong analgesics, the views of their families, and variation in patient preferences with age. They also noted variability across populations with regard to individual side effects. They concluded that, with regard to different analgesics at the stage of initiation of pain management, there was major variation in how much people value the options.

FEASIBILITY ./ RESOURCE USE

How large are the resource requirements?

Major ☐ Minor ☐ Uncertai Yes

Is the option feasible to implement?

Yes ☐ No ☐ Uncertain Yes

Source:[12]	Number of Countries Where Available for Free	Number of Countries Where Available	Price of one 30-Day Opioid Treatment			
			Median	IQR	Mean	SD
Morphine oral immediate release (tablet, capsule)	11	35	$ 49.70	$ 80.50	$ 78.50	$ 92.00
Morphine oral slow release (tablet, capsule)	15	44	$ 56.80	$ 110.50	$ 83.80	$ 90.70
Morphine oral (liquid)	9	26	$ 41.90	$ 96.50	$ 67.58	$ 63.60
Morphine injectable (ampoule)	19	49	$ 88.50	$ 167.30	$ 167.20	$ 225.30
Fentanyl (transdermal patch)	15	47	$ 81.20	$ 263.40	$ 144.60	$ 154.10
Methadone oral solid (tablet, capsule)	9	22	$ 26.50	$ 38.30	$ 40.50	$ 29.10
Methadone oral (liquid)	9	26	$ 13.10	$ 70.90	$ 58.80	$ 103.40
Oxycodone oral immediate release (tablet, capsule)	6	19	$ 202.90	$ 156.80	$ 198.10	$ 125.20
Oxycodone oral slow release (tablet, capsule)	6	21	$ 237.20	$ 473.70	$ 312.40	$ 252.10
Hydromorphone oral immediate release (tablet, capsule)	2	7	$ 103.45	$ 115.60	$ 78.30	$ 61.50
Hydromorphone oral slow release (tablet, capsule)	3	10	$ 14.97	$ 89.10	$ 51.60	$ 54.90
Hydromorphone oral (liquid)	0	2	$ 146.20	NA	$ 150.30	$ 146.20
Hydromorphone injectable (ampoule)	2	4	$ 101.10	NA	$ 73.20	$ 101.10

	Would the option improve equity in health? Yes No Uncertai Yes ☐ ☐	**Research evidence** None presented. **Additional considerations** The GDG believe that the availability of these options to patients would increase equity since the majority of the world's population has poor access and availability to the medications. The GDG note that in many countries, only the capital city has access and availability for some patients; in the rest of the country, these medications may be unavailable. Furthermore, they note that since there is variation in patients' response to specific analgesic medications, there should be multiple medications available that are appropriate for all pain intensities. The GDG also bore in mind the risk of unintended consequences. They noted that balanced regulations of these strong opioid medications, which balance the necessity of their availability to patients who need them with the necessity of tackling their misuse, are possible. Recommendations on how to achieve this balance are presented in other WHO documents [13].

Recommendation	**Current recommendation:** Previous guidelines recommended 'sequential use of drugs': first a non-opioid with or without an adjuvant; then if pain is not relieved, 'an opioid for mild to moderate pain should be added'; if this combination 'fails to relieve the pain, an opioid for moderate to severe pain should be substituted'. **New (draft) recommendation:** In adults (including the older person) and adolescents with pain related to active cancer, NSAIDs, paracetamol, and opioids (alone or in combination) should be used at the stage of initiation of pain management depending on clinical assessment and pain severity in order to achieve rapid, effective and safe pain control.
Strength of Recommendation	**Strong**
Quality of Evidence	➢ **Low** [Pain (critical) = very low Confusion = moderate (morphine vs. oxycodone CR) others omitted for no data]
Justification	The quality of the RCT evidence concerning the selection of a particular type of analgesic over others was low. The GDG were concerned that limiting a recommendation on this basis to a conditional recommendation would belie the strength of informed medical consensus on the administration of appropriate-strength analgesics to patients who need them, and would thus risk exacerbating widespread misconceptions in this area and concomitant lack of access and availability to many of these medications. Furthermore the GDG felt strongly that a range of weak and strong analgesic medications should be available to adult, adolescent, and older persons with cancer pain since there is variation in individuals' responses to specific analgesic medications, and wanted to be clear with a strong recommendation that having only a small selection was inadequate for appropriate treatment of mild, moderate, and severe pain.

	The GDG also saw this question as an opportunity to clarify that patients should be started on an analgesic that is appropriate to their level of pain, which was not clear from the 1996 guidelines which led to a common belief that patients should be started only on the first step of the cancer pain analgesic ladder, i.e. a non-opioid +/- adjuvant.
Subgroup considerations	
Implementation considerations [incl. M&E]	
Research priorities	

1.2. In adults (including older persons) and adolescents with pain related to active cancer, are there any differences between opioids for maintenance of therapy in order to achieve rapid, effective and safe pain control?

Thirty-eight eligible RCTs evaluated outcomes of interest among people with cancer who were being managed for their cancer pain.[14-51] However, few trials clearly distinguished between patients at pain management initiation and those on maintenance treatment. The determination of whether all or most patients included in a study were in the maintenance stage of their pain management treatment was, in part, a matter of judgment. The systematic review team divided Key Question 1.2 into two sections: opioids versus placebo (or no opioids) and comparison of analgesics.

Two of the RCTs compared opioids to placebo treatments (one of which also included a comparison between analgesics).[19,28]

1.2.1. Opioids Versus Placebo

The two placebo-controlled RCTs evaluated Celecoxib, Codeine, and Codeine + Ibuprofen, (see Evidence Profile 1.2.1).[19,28]

One trial reported no significant difference in pain relief speed (time to pain relief) between both codeine and combined codeine and ibuprofen versus placebo; in fact placebo was favored over codeine alone (low strength of evidence). The difference between codeine and placebo was an increase of 20 minutes (95% CI -23, 63). The difference between codeine plus ibuprofen and placebo was 0 minutes (95% CI -28, 28).

The same trial, however, reported that both codeine and combined codeine and ibuprofen resulted in longer pain reduction maintenance compared with placebo (low strength of evidence). For codeine, this was 2.1 hours (0.7, 3.5) and for codeine plus ibuprofen this was 3.5 hours (95% CI 1.5, 5.5).

One trial found no significant difference in quality of life, as measured by the EORTC QTQ-C30, between celecoxib and placebo (very low strength of evidence). There was a difference of 2 on a scale of 0 to 100 [best], but no further data were reported.

The studies did not report specifically on respiratory depression or sedation.

The studies did not report data to allow evaluation of subgroup differences.

Evidence Profile 1.2.1. Analgesics vs. Placebo During Maintenance of Pain Management

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Analgesics	Placebo	Relative (95% CI)	Absolute (95% CI)		
Pain relief												
									See Network Meta-Analysis			CRITICAL
Pain relief speed (follow up: 6 hours)												
1 [1]	RCT	not serious	N/A	not serious	serious [A]	single study	36	18	**Codeine Diff 20** (-23, 63) min; **Codeine + Ibuprofen Diff 0** (-28, 28)		Low	IMPORTANT
Pain reduction maintenance (follow up: 6 hours)												
1 [1]	RCT	not serious	N/A	not serious	serious [A]	single study	36	18	**Codeine Diff 2.1** (0.7, 3.5) hr; **Codeine + Ibuprofen Diff 3.5** (1.5, 5.5) hr, favoring opioids		Low	CRITICAL
Quality of life (follow up: 20 weeks, assessed with EORTC QLQ-C30l Scale from: 0 to 100 [best] [B])												
1 [2]	RCT	serious [C]	N/A	serious [E]	serious [A]	single study	81	80	**Celoxicab: 2 (NS)** [D]		Very Low	CRITICAL
Functional outcomes												
0									not estimable			IMPORTANT
Adverse events: Respiratory depression												
0									not estimable			IMPORTANT
Adverse events: Sedation												
0									not estimable			IMPORTANT

Abbreviations: AE: *adverse events;* ***CI:*** *Confidence interval;* ***CR****: controlled release;* ***Diff:*** *Difference (between interventions);* ***EORTC QLQ-C30****: European Organization for Research and Treatment of Cancer Quality Of Life Questionnaire Core-30;* ***NS****: not statistically significant;* ***RCT:*** *randomized controlled trials.*

Explanations

A. Small sample size. Wide confidence intervals for pain relief speed.

B. Scales transformed to 0 to 100, as necessary.
C. No variance data reported
D. No further data reported.
E. An older measure of quality of life that mixes concepts of both quality of life and functional outcomes.

Trials

1. Chen Y, Zhu W, Liang H, Wu G. The analgesic effect of ibuprofen-codeine sustained release tablets on postoperative and cancer pain. Chinese Journal of Clinical Rehabilitation; 2003.
2. Koch A., Bergman B., Holmberg E., et al. Effect of celecoxib on survival in patients with advanced non-small cell lung cancer: a double blind randomised clinical phase III trial (CYCLUS study) by the Swedish Lung Cancer Study Group.. 2011.

1.2.2. Comparison of Analgesics

Readers are encouraged to refer to Annex 6 Network Meta Analysis (NMA) for further analysis from direct and indirect evidence on the 'effective pain relief' outcome

Twenty-six trials were included in the direct comparisons for outcomes other than pain relief and evaluated 14 different analgesics: Buprenorphine, Butorphanol, Celecoxib, Codeine, Codeine + Ibuprofen, Dexketoprofen trometamol, Dezocine, Diclofenac, Hydromorphone CR, Kadian, Kapanol, Ketorolac, Morphine CR, Morphine IR, Oxycodone CR, Tapentadol CR, and Tramadol (see Evidence Profile 1.2.2). [14-27,29-40]

From the direct evidence, four trials evaluated speed of pain relief, providing low strength of evidence of no significant difference among Codeine, Codeine + Ibuprofen, Diclofenac, Ketorolac, Morphine CR, Morphine IR, and Oxycodone CR. The studies evaluated different outcomes, which ranged from minutes to days.

Five trials evaluated duration of maintenance of pain reduction. There is low strength of evidence of no significant differences among the interventions (Codeine, Codeine + Ibuprofen, Diclofenac, Kadian (every 12 hours), Ketorolac, Morphine CR, and Morphine IR). One trial reported that Kadian every 24 hours had longer mean time to remedication (16 hr) than Kadian every 12 hours (9.1 hr) or Morphine CR (8.7 hr).
No eligible trials reported on quality of life.

Two trials reported on functional outcomes. There is low strength of evidence of no significant difference between Morphine and Methadone (on the Karnofsky Performance Scale), but favoring Ketorolac over Dexketoprofen trometamol.

Only one of the trials explicitly discussed respiratory depression (in fact "respiratory failure") among their adverse events, providing very low strength of evidence. A single occurrence was reported among 62 people taking tapentadol, but none with morphine SR.

Seventeen trials provided very low strength of evidence overall regarding relative risks of sedation. The studies were heterogeneous in definitions of sedation, which was likely largely responsible for large heterogeneity in the reported rates of sedation. See Evidence Profile 1.2.2 for details. Only one pair of medications were compared by more than one trial. Two trials provided low quality evidence of no difference comparing risk of sedation between fentanyl and morphine SR yielding a RR of 0.88 (95% CI 0.52, 1.48).

The studies did not report data to allow evaluation of subgroup differences.

Evidence Profile 1.2.2. Comparison of Analgesics During Maintenance of Pain Management

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Analgesics**	**Analgesics**	**Relative (95% CI)**	**Absolute (95% CI)**		
Pain relief												
									See Network Meta-Analysis			CRITICAL
Pain relief speed (follow up: range 12 hours to 12 days)												
4 [1,2,3,4]	RCT	serious [A]	not serious	not serious	not serious	variable outcomes, poor reporting	332 across interventions		**NS** [B]		Low	IMPORTANT
Pain reduction maintenance (follow up: range 6 hours to 7 days)												
4 [1,3,5,7]	RCT	serious [A]	not serious	not serious	not serious	variable outcomes, poor reporting	602 across interventions		**Mostly NS** [C]		Low	CRITICAL
Quality of life												
0									not estimable			CRITICAL
Functional outcomes (follow up: range 7 days to 14 days; assessed with: KPS; Scale: 0 to 100 [best]*)												
2 [8,9]	RCT	serious [D]	N/A	not serious	not serious	sparse	173 across interventions		**KPS 4.9** [E] (NS) **KPS 3.0** [F] (-0.8, 6.8)		Low	IMPORTANT
Adverse Events: Respiratory depression (14 days, respiratory failure)												
1 [10]	RCT	not serious	N/A	serious [G]	serious [H]	single study	**Tapentadol** 1/62 (1.6%)	**Morphine SR** 0/31 (0%)	**RR 1.52** (0.06, 36.4)	**10 more per 1000 with tapentadol** (from 49 fewer to 65 more)	Very Low	IMPORTANT
Adverse Events: Sedation (follow up: range 3 days to 20 weeks)												
17 [6,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26]	RCT	serious [I]	serious [J]	serious [K]	none	sparse [L]	1748 across interventions		**NS overall** [M]		Very Low	IMPORTANT
2 [20, 28]	RCT	serious [N]	not serious	not serious	serious [H]	none	**Fentanyl** 22/142 (17% [O])	**Morphine SR** 25/142 (21% [O])	**RR 0.88** (0.52, 1.48)	**25 more per 1000 with morphine** (from 99 fewer to 99 more)	Low	IMPORTANT

***Abbreviations: CI**: confidence interval; **KPS:** Karnofsky Performance Status scale**; NS**: not statistically significant; **RCT**: randomized controlled trial(s).*

Explanations

A. Poor reporting of outcome.
B. All 4 studies NS. Data too variable and incompletely reported to allow meta-analysis:
Ketorolac 30 mg 1.3 hr, Ketorolac 10 mg 1.4 hr, Diclofenac 1.7 hr; P=0.209 across interventions.
Morphine CR 2 days (range 1-9 days), Oxycodone CR 2 days (range 1-10 days).
Codeine + Ibuprofen vs. Codeine: Difference = 12 hours (95% CI -6.4, 30.4), nominally favoring codeine + ibuprofen.
Morphine SR vs. Morphine IR: Difference = 0.4 days (95% CI -0.5, 1.3), nominally favoring morphine SR.
C. Data too variable and incompletely reported to allow meta-analysis.
1 study: Kadian every 24 hours had longer mean time to remedication (16 hr) than Kadian every 12 hours (9.1 hr) or Morphine CR (8.7 hr); P = 0.001.
2 studies: Ketorolac vs. Diclofenac:
Ketorolac 4.4 days (range 0-8 days), Diclofenac 4.2 days (range 0-8 days); NS. Duration of pain reduction efficacy.
Ketorlac 30 mg 5.4 hours, Ketorolac 10 mg 5.5 hours, Diclofenac 5.0 hours. No further data. Duration of positive analog pain intensity difference.
1 study: Codeine + Ibuprofen vs. Codeine: Difference = 1.4 hours (95% CI -1.0, 3.8), nominally favoring codeine + ibuprofen. Maintaining time.
D. In 1 study high attrition and unblinded outcome assessors.
E. Favoring Morphine over Methadone.
F. Favoring Ketorolac over Dexketoprofen
G. Unclear what is meant by respiratory failure.
H. Wide confidence interval.
I. High attrition, lack of blinding.
J. Highly heterogeneous rates across studies (see Explanation M).
K. Various specific outcomes.
L. Most comparisons evaluated by only a single study.
M. All NS within study. However, data too heterogeneous to allow meta-analyses (various definitions of sedation [sedation, somnolence, drowsiness, tiredness], 10 interventions : Fentanyl TD 3 studies 6-14%, Hydromorphone CR 1 study 7%, Methadone 2 studies 15-27%, Morphine CR 6 studies 6-19%, Morphine IR 3 studies 17-70%, Oxycodone CR 1 study 59%, Oxycodone IR 2 studies 32-65%, Tapentadol 1 study 4%, Tramadol + Fentanyl TD 1 study 6%, Tramadol + Tapentadol 1 study 9%.
N. Lack of blinding.
O. Meta-analyzed value.

Trials

1. Chen Y, Zhu W,Liang H,Wu G. The analgesic effect of ibuprofen-codeine sustained release tablets on postoperative and cancer pain. Chinese Journal of Clinical Rehabilitation; 2003.
2. Mucci-LoRusso, P., Berman, B. S., Silberstein, P. T., et al. Controlled-release oxycodone compared with controlled-release morphine in the treatment of cancer pain: a randomized, double-blind, parallel-group study. Eur J Pain; 1998.
3. Minotti, V., Betti, M., Ciccarese, G., Fumi, G., Tonato, M., Del Favero, A. A double-blind study comparing two single-dose regimens of ketorolac with diclofenac in pain due to cancer. Pharmacotherapy; May-Jun 1998.
4. Klepstad, P., Kaasa, S., Jystad, A., Hval, B., Borchgrevink, P. C. Immediate- or sustained-release morphine for dose finding during start of morphine to cancer patients: a randomized, double-blind trial. Pain; Jan 2003.
5. Pannuti, F., Robustelli della Cuna, G., Ventaffrida, V., Strocchi, E., Camaggi, C. M. A double-blind evaluation of the analgesic efficacy and toxicity of oral ketorolac and diclofenac in cancer pain. The TD/10 recordati Protocol Study Group. Tumori; Mar-Apr 1999.
6. Finn, J. W., Walsh, T. D., MacDonald, N., Bruera, E., Krebs, L. U., Shepard, K. V. Placebo-blinded study of morphine sulfate sustained-release tablets and immediate-release morphine sulfate solution in outpatients with chronic pain due to advanced cancer. J Clin Oncol; May 1993.
7. Broomhead, A., Kerr, R., Tester, W., et al. Comparison of a once-a-day sustained-release morphine formulation with standard oral morphine treatment for cancer pain. J Pain Symptom Manage; Aug 1997.
8. Ventafridda, V., Ripamonti, C., Bianchi, M., Sbanotto, A., De Conno, F. A randomized study on oral administration of morphine and methadone in the treatment of cancer pain. J Pain Symptom Manage; Fall 1986.
9. Rodriguez, M. J., Contreras, D., Galvez, R., et al. Double-blind evaluation of short-term analgesic efficacy of orally administered dexketoprofen trometamol and ketorolac in bone cancer pain. Pain; Jul 2003.
10. Poulain, P. A study to evaluate the effectiveness and safety of CG5503 (tapentadol) in the treatment of chronic tumor-related pain compared with placebo and morphine. ClinicalTrials.gov; 2010.
11. Wilder-Smith, C. H., Schimke, J., Osterwalder, B., Senn, H. J. Oral tramadol, a mu-opioid agonist and monoamine reuptake-blocker, and morphine for strong cancer-related pain. Ann Oncol; Feb 1994.
12. Walsh, T. D., MacDonald, N., Bruera, E., Shepard, K. V., Michaud, M., Zanes, R. A controlled study of sustained-release morphine sulfate tablets in chronic pain from advanced cancer. Am J Clin Oncol; Jun 1992.
13. Kalso, E., Vainio, A. Morphine and oxycodone hydrochloride in the management of cancer pain. Clin Pharmacol Ther; May 1990.
14. Beaver, W. T., Wallenstein, S. L., Houde, R. W., Rogers, A. A clinical comparison of the analgesic effects of methadone and morphine administered intramuscularly, and of orally and parenterally administered methadone. Clin Pharmacol Ther; May-Jun 1967.
15. Arkinstall, W. W., Goughnour, B. R., White, J. A., Stewart, J. H. Control of severe pain with sustained-release morphine tablets v. oral morphine solution. Cmaj; Mar 15 1989.
16. Wong, J. O., Chiu, G. L., Tsao, C. J., Chang, C. L. Comparison of oral controlled-release morphine with transdermal fentanyl in terminal cancer pain. Acta Anaesthesiol Sin; Mar 1997.
17. Mercadante, S., Casuccio, A., Agnello, A., Serretta, R., Calderone, L., Barresi, L. Morphine versus methadone in the pain treatment of advanced-cancer patients followed up at home. J Clin Oncol; Nov 1998.
18. Heiskanen, T., Kalso, E. Controlled-release oxycodone and morphine in cancer related pain. Pain; Oct 1997.
19. Hagen, N. A., Babul, N. Comparative clinical efficacy and safety of a novel controlled-release oxycodone formulation and controlled-release hydromorphone in the treatment of cancer pain. Cancer; Apr 01 1997.
20. Bruera, E., Belzile, M., Pituskin, E., et al. Randomized, double-blind, cross-over trial comparing safety and efficacy of oral controlled-release oxycodone with controlled-release morphine in patients with cancer pain. J Clin Oncol; Oct 1998.
21. Ahmedzai, S., Brooks, D. Transdermal fentanyl versus sustained-release oral morphine in cancer pain: preference, efficacy, and quality of life. The TTS-Fentanyl Comparative Trial Group. J Pain Symptom Manage; May 1997.
22. Marinangeli, F., Ciccozzi, A., Aloisio, L., et al. Improved cancer pain treatment using combined fentanyl-TTS and tramadol. Pain Pract; Dec 2007.
23. Gabrail, N. Y., Dvergsten, C., Ahdieh, H. Establishing the dosage equivalency of oxymorphone extended release and oxycodone controlled release in patients with cancer pain: a randomized controlled study. Curr Med Res Opin; Jun 2004.
24. Kress, H. G., Koch, E. D., Kosturski, H., et al. Direct conversion from tramadol to tapentadol prolonged release for moderate to severe, chronic malignant tumour-related pain. Eur J Pain; Oct 2016.
25. Homsi, J., Walsh, D., Lasheen, W., et al. A comparative study of 2 sustained-release morphine preparations for pain in advanced cancer. Am J Hosp Palliat Care; Mar 2010.
26. Hanna, M., Thipphawong, J. A randomized, double-blind comparison of OROS(R) hydromorphone and controlled-release morphine for the control of chronic cancer pain. BMC Palliat Care; Oct 31 2008.

Evidence-to-Decision table 1.2

In adults (including older persons) and adolescents with pain related to active cancer, are there any differences between opioids for maintenance of therapy in order to achieve rapid, effective and safe pain control?

POPULATION:	Adults (including older persons) and adolescents with cancer-related pain
INTERVENTION:	Opioids
COMPARISON:	Opioids, placebo Multiple comparisons
MAIN OUTCOMES:	• Pain relief • Pain relief speed • Pain relief maintenance • Quality of life (QoL) • Functional outcomes • Respiratory depression (adverse event) • Sedation (adverse event)
STRATIFICATIONS:	• Age (adults, older persons, adolescents, children) • History of substance abuse • Refractory pain
SETTING:	All
PERSPECTIVE:	Population

For full analysis, please see Annex 6 for the Network Meta Analysis which primarily addresses this question

Background:

- Recent estimates state that 25.5 million people died in 2015 in serious health-related suffering, of which 80% lived in countries that lack access to palliative care and pain relief [6]. Cancer was responsible for 8.8 million deaths in 2015 [7]. Expert opinion and data from country experiences from several low-income countries suggest that approximately 80% of people dying from cancer experience moderate or severe pain lasting on average 90 days[6]. A recent systematic review of published evidence reports a similarly high figure that 66.4% of patients with advanced, metastatic, or terminal disease experience pain [52].

Current WHO recommendation:

- Analgesics should be given "by the mouth", "by the clock", "by the ladder", "for the individual", with "attention to detail".
    - By the mouth – Where possible, analgesics should be given by the mouth. Rectal suppositories (or alternatively, continuous subcutaneous infusion) may be preferred in patients with dysphagia , uncontrolled vomiting, or gastrointestinal obstruction.
    - By the clock – Analgesics should be given at fixed intervals of time. The dose should be gradually increased until the patient is comfortable. The next dose should be given before the effect of the previous dose has worn off.
    - By the ladder – "The first step is a non-opioid. If this does not relieve the pain, an opioid for mild to moderate pain should be added. When an opioid for mild to moderate pain in combination with a non-opioid fails to relieve the pain, an opioid for moderate to severe pain should be substituted. Only one drug from each of the groups should be used at the same time. Adjuvant drugs should be given for specific indications. If a drug ceases to be effective, do not switch to an alternative drug of similar efficacy … but prescribe a drug that is definitely stronger."
    - For the individual – The right dose is the dose that relieves the patient's pain.
    - With attention to detail – The first and last doses of the day should be linked to the patient's waking time and bedtime. Ideally, the patient's analgesic medication regimen should be written out in full for the patient and their family to work from.
- Previous guidelines recommend that dose takes into account the associated development of tolerance and possible development of physical dependence. Tolerance is characterized by decreased efficacy and

		duration of action of the opioid medication with repeated administration, requiring an increased dose to maintain the analgesic effect. It states that in practice, physical dependence and tolerance do not prevent the effective use of these medications. Patients with stable disease often remain on a stable dose for weeks or months. Previous guidelines discount the development of psychological dependence in cancer patients as a result of receiving opioids for relief of pain. The guidelines also recommend that the regimen offered accounts for disease-induced alterations in opioid pharmacokinetics, especially in cirrhosis and renal failure. If a patient appears to be intolerant to morphine, an alternative strong opioid is recommended. • Choice of analgesic – The array of specific non-opioids considered included acetylsalicylic acid (ASA) 500-600mg every 4-6 hours, other NSAIDs (such as those on essential medicines lists, e.g. ibuprofen 400mg every 4-6 hours and indomethacin 25mg every 6 hours), and paracetamol 650-1000mg every 4-6 hours. Specific choice from this selection "will depend on factors such as local availability and cost." The guidelines take note of typical contraindications such as gastric irritation, toxicities, hypersensitivity reactions, and other potential adverse effects of these medications, and notes the maximum dosages for each of the medications to avoid excess adverse effects: maximum 4g of ASA per day, maximum 6g paracetamol per day, maximum 3g ibuprofen per day, maximum 200mg indomethacin per day. The 1996 guidelines state that the initial dose of an opioid for moderate to severe pain depends mainly on the patient's previous medication. For those who have previously received 60-100mg of codeine by mouth, they state that a starting dose of 10-15mg of morphine is usually adequate. Dose should be halved if the patient becomes somnolent after the first dose and is free of pain. If after 24 hours on this medication, Not all medications were discussed with regards the maintenance of pain management. Dosages for medications should be increased according to clinical assessment. The recommended starting regimens for each medication discussed are: • Codeine by mouth 30-120mg every four hours. • Morphine by simple aqueous solution or tablet every four hours, or by slow release tablets every 12 hours. The correct dose is "the dose that works" to relieve a patient's pain. Typical starting dose 10-15mg. • Standardised opium – no standard dose given. • Tramadol usual dose by mouth 50-100mg every 4-6 hours. • Hydromorphone usual starting dose 1-2mg by mouth or 1mg by subcutaneous injection, analgesia lasting 3-4 hours. Doses of hydromorphone by injection are typically 1/3 to ½ of the previously satisfactory oral dose. • Methadone 5-10mg by mouth or by subcutaneous injection, analgesia lasting 6-12 hours. • Levorphanol usual starting dose 1-2mg by mouth four times per day. Half dose for injection. • Pethidine 50-100mg may be given every three hours as a starting dose, or more frequently in patients with severe cancer pain.

		• Oxycodone usual starting dose 5-15mg by mouth or rectally, analgesia lasting 3-5 hours. • Buprenorphine dose to account for its 60 times greater potency than orally administered morphine. When pain is no longer controlled by buprenorphine, 100 times the previously administered total daily dose of buprenorphine should be given of oral morphine sulfate in a four hourly regimen instead. It states that most patients' pain is satisfactorily controlled on an 8 hour regimen. • Night doses – medications should be given through the night or in a larger dose at bedtime to sustain the plasma level of the medication within the effective range. Many patients with a double dose of morphine do not need a further dose until morning. A double dose is not necessary with slow release preparations of morphine or with longer0acting medications such as methadone and buprenorphine.

	CRITERIA	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** Yes	Expert opinion and data from country experiences from several low-income countries suggest that approximately 80% of the millions of people dying from cancer each year experience moderate or severe pain lasting on average 90 days, most of whom lived in countries with inadequate access and availability of adequate pain management[6]. Previous WHO guidelines were issued in 1996. Up to date guidance is needed in order to overcome attitude and knowledge barriers to the delivery of adequate pain management.[9]

BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Yes No Uncertain Yes	Thirty-eight trials provided data for outcomes of interest. **Readers are encouraged to refer to Annex 6 Network Meta Analysis (NMA) for further analysis on the 'effective pain relief' outcome** For the direct evidence, 27 randomized controlled trials compared analgesics with either other analgesics or placebo (which were all analyzed together); 26 of these compared analgesics to each other. The trials evaluated 14 classes of analgesics (high-potency opioid, high-potency opioid + antidepressant, high-potency opioid + NSAID, low-potency opioid, high-potency opioid + opioid antagonist, high-potency opioid + paracetamol, low-potency opioid + NSAID, low-potency opioid + paracetamol, high-potency opioid + low-potency opioid, NSAID, NSAID + antidepressant, cannabinoid, and other non-opioid analgesic). 12 studies were conducted in older persons, no study was conducted in only adolescents. **BENEFITS and HARMS** • Direct and indirect evidence from the NMA of **6 trials** provide **low strength of evidence** that the following analgesic classes **may make no difference to pain relief** than the alternative: ○ **Low-potency opioid** may be no better than **low-potency opioid + paracetamol** (OR 1.40; 95% CI 0.55, 3.55) ○ **High-potency opioid + paracetamol** may be no better than **low-potency opioid + paracetamol** (OR 1.25; 95% CI 0.51, 3.09) ○ **High-potency opioid + paracetamol** may be no better than **low-potency opioid** (OR 0.89; 95% CI 0.35, 2.27) All other comparisons have very low strength of evidence. • Direct and indirect evidence from the NMA of **13 trials** provide **high strength of evidence** that **high-potency opioid + NSAID reduces pain better** than: ○ **High-potency opioid + opioid antagonist** (SMD -1.16; 95% CI -1.90,-0.41) ○ **Non-opioid analgesic (dipyrone)** (SMD -1.16; 95% CI -1.72, -0.60) ○ **High-potency opioid (alone)** (SMD -0.96; 95% CI -1.36, -0.56) There is **moderate strength of evidence** for **reducing pain** regarding comparisons of the following analgesic classes: ○ **High-potency opioid + NSAID** is **probably better** than **high-potency opioid + low-potency opioid** (SMD -0.83; 95% CI -1.28, -0.37) ○ **High-potency opioid + NSAID** is **probably better** than **cannabinoid** (SMD -0.77; 95% CI -1.43, -0.10) ○ **Cannabinoid** is **probably no better** than **non-opioid analgesic (dipyrone)** (SMD -0.39; 95% CI -1.06, 0.27) ○ **NSAID (alone)** is **probably no better** than **NSAID + antidepressant** (SMD -0.37; 95% CI -0.81; 0.06) ○ **Non-opioid analgesic (dipyrone)** is **probably no better** than **high-potency opioid** (SMD 0.20; 95% CI -0.20, 0.59) There is **low strength of evidence** for **reducing pain** regarding comparisons of the following analgesic classes: ○ **High-potency opioid + NSAID may be better** than **low-potency opioid** (SMD -0.73; 95% CI -1.29, -0.18) ○ **Low-potency opioid may be no better** than **non-opioid analgesic (dipyrone)** (SMD -0.43; 95% CI -0.98, 0.13) ○ **Cannabinoid may be no better** than **high-potency opioid + opioid antagonist** (SMD -0.39; 95% CI -1.22, 0.44) ○ **High-potency opioid + low-potency opioid may be no better** than **non-opioid analgesic (dipyrone)** (SMD -0.33; 95% CI -0.79, 0.12)

- **NSAID + antidepressant** may be no better than **Low-potency opioid + NSAID** and (SMD 0.09; 95% CI -0.34, 0.52)

The evidence for the choice between the following analgesic classes was **very low:**

- **High-potency opioid** and **high-potency opioid + opioid antagonist** (SMD -0.20; 95% CI -0.83, 0.44)
- **Cannabinoid** and **high-potency opioid** (SMD -0.19; 95% CI -0.73, 0.34)
- **High-potency opioid + low-potency opioid** and **high-potency opioid** (SMD -0.13; 95 CI -0.36, 0.09)
- **Low-potency opioid + NSAID** and **high-potency opioid + low-potency opioid** (SMD -0.12; 95% CI -0.73, 0.49)
- **NSAID + antidepressant** and **NSAID + low-potency opioid** (SMD -0.09; 95% CI -0.52, 0.34)
- **Low-potency opioid** and **cannabinoid** (SMD -0.03; 95% CI -0.52, 0.45)
- **Non-opioid analgesic (dipyrone)** and **high-potency opioid + opioid antagonist (dipyrone)** (SMD 0.00; 95% CI -0.74, 0.75)

- From direct evidence, f**our trials** provided **low strength of evidence** of **no significant difference on speed of pain relief** among Codeine, Codeine + Ibuprofen, Diclofenac, Ketorolac, Morphine CR, Morphine IR, and Oxycodone CR. The studies evaluated different outcomes, which ranged from minutes to days.
- **Four trials** provided **low strength of evidence** of **no significant differences of duration of maintenance of pain reduction among the interventions** (Codeine, Codeine + Ibuprofen, Diclofenac, Kadian (every 12 hours), Ketorolac, Morphine CR, and Morphine IR). One trial reported that Kadian every 24 hours had longer mean time to remedication (16 hr) than Kadian every 12 hours (9.1 hr) or Morphine CR (8.7 hr).
- **No trial** reported on **quality of life**.
- **Two trials** provided **low strength of evidence** of **no significant difference for functional outcomes** between Morphine and Methadone (on the Karnofsky Performance Scale), but favoring Ketorolac over Dexketoprofen trometamol.
- **One trial** provided **very low strength of evidence** reported on respiratory depression, **reporting a single occurrence** of "respiratory failure" among 62 people taking tapentadol, but none with morphine SR.
- **Seventeen trials** provided **very low strength of evidence** reported on sedation, using various definitions within studies (sedation, somnolence, drowsiness, tiredness). **The rates of sedation were heterogeneous across 10 interventions**: Fentanyl TD (3 trials) 6-14%, Hydromorphone CR (1 trial) 7%, Methadone (2 trials) 15-27%, Morphine CR (6 trials) 6-19%, Morphine IR (3 trials) 17-70%, Oxycodone CR (1 trial) 59%, Oxycodone IR (2 trials) 32-65%, Tapentadol (1 trial) 4%, Tramadol + Fentanyl TD (1 trial) 6%, Tramadol + Tapentadol (1 trial 9%). **Two trials** provided **low strength of evidence** comparing risk of sedation between **fentanyl and morphine SR** yielding a RR of 0.88 (95% CI 0.52, 1.48), **nominally favoring fentanyl**.

STRATIFICATIONS

- Stratification of the analysis of all analgesics separate for adolescents and older persons provided very uncertain results for pain relief (due to the small number of studies) which however appear to be in line with the findings from the analysis of all studies
- Studies provide no data regarding history of substance abuse or refractory pain.

SUMMARY

		Combination high-potency opioid and NSAID reduces pain better than alternative analgesics. Choice of analgesic may make little or no difference in speed of pain relief, duration of maintenance of pain reduction, or functional outcomes. Fentanyl may cause slightly less sedation than sustained-release morphine.

ACCEPTABILITY & PREFERENCES	**Is there important uncertainty or variability about how much people value the options?** Major variability [ ] Minor variability [Yes] Uncertain [ ] **Is the option acceptable to key stakeholders?** Yes [Yes] No [ ] Uncertain [ ]	**<u>Research Evidence:</u>** The systematic review reveals some differences between the medications with regards to adverse effects. The GDG agreed that all options should be acceptable to key stakeholders such as clinicians and policymakers, but ill-founded opiophobia continues to be an issue with acceptability in many settings worldwide[11]. **<u>Additional considerations</u>** The GDG acknowledged that some patients will prefer some medications over others due to differences in adverse event profiles or contraindications for certain medications. To match this important preference, the GDG implored that there be a variety of appropriate treatments available to patients to meet their variegated clinical needs, including at least one fast acting strong opioid medication. However, the GDG also acknowledged that many differences between opioid medications are often overstated, as evidenced by the guidelines' systematic review. Therefore the cost of medications should be an important factor in decisions to make certain medications available. In low-resource settings, cheaper medications should be preferred as the clinical differences between those and the more expensive medications are small.

FEASIBILITY ./ RESOURCE USE

How large are the resource requirements?

Major	Minor	Uncertain
	Yes	

Is the option feasible to implement?

Yes	No	Uncertain
Yes		

Source:[12]	Number of Countries Where Available for Free	Number of Countries Where Available	Price of one 30-Day Opioid Treatment			
			Median	**IQR**	**Mean**	**SD**
Morphine oral immediate release (tablet, capsule)	11	35	$ 49.70	$ 80.50	$ 78.50	$ 92.00
Morphine oral slow release (tablet, capsule)	15	44	$ 56.80	$ 110.50	$ 83.80	$ 90.70
Morphine oral (liquid)	9	26	$ 41.90	$ 96.50	$ 67.58	$ 63.60
Morphine injectable (ampoule)	19	49	$ 88.50	$ 167.30	$ 167.20	$ 225.30
Fentanyl (transdermal patch)	15	47	$ 81.20	$ 263.40	$ 144.60	$ 154.10
Methadone oral solid (tablet, capsule)	9	22	$ 26.50	$ 38.30	$ 40.50	$ 29.10
Methadone oral (liquid)	9	26	$ 13.10	$ 70.90	$ 58.80	$ 103.40
Oxycodone oral immediate release (tablet, capsule)	6	19	$ 202.90	$ 156.80	$ 198.10	$ 125.20
Oxycodone oral slow release (tablet, capsule)	6	21	$ 237.20	$ 473.70	$ 312.40	$ 252.10
Hydromorphone oral immediate release (tablet, capsule)	2	7	$ 103.45	$ 115.60	$ 78.30	$ 61.50
Hydromorphone oral slow release (tablet, capsule)	3	10	$ 14.97	$ 89.10	$ 51.60	$ 54.90
Hydromorphone oral (liquid)	0	2	$ 146.20	NA	$ 150.30	$ 146.20
Hydromorphone injectable (ampoule)	2	4	$ 101.10	NA	$ 73.20	$ 101.10

	Would the option improve equity in health? Yes No Uncertain Yes ☐ ☐	**<u>Research evidence</u>** None presented. **<u>Additional considerations</u>** The GDG believe that the availability of these options to patients would increase equity since the majority of the world's population has poor access and availability to the medications. The GDG note that in many countries, only the capital city has access and availability for some patients; in the rest of the country, these medications may be unavailable. Furthermore, they note that since there is variation in patients' response to specific analgesic medications, there should be multiple medications available that are appropriate for all pain intensities. Improvements in equity are contingent on multiple factors, including the availability of affordable medications. The GDG reiterated their view that cheap, effective medications should be available to all patients in need of pain management and if there is no obvious best analgesic for a patient, the cheapest medication should be used. The GDG also bore in mind the risk of unintended consequences. They noted that balanced regulations of these strong analgesics, which balance the necessity of their availability to patients who need them with the necessity of tackling their misuse, are possible. Recommendations on how to achieve this balance are presented in other WHO documents[13].

Recommendation

Current recommendation:

- Analgesics should be given "by the mouth", "by the clock", "by the ladder", "for the individual", with "attention to detail".
    - By the mouth – Where possible, analgesics should be given by the mouth. Rectal suppositories (or alternatively, continuous subcutaneous infusion) may be preferred in patients with dysphagia , uncontrolled vomiting, or gastrointestinal obstruction.
    - By the clock – Analgesics should be given at fixed intervals of time. The dose should be gradually increased until the patient is comfortable. The next dose should be given before the effect of the previous dose has worn off.
    - By the ladder – "The first step is a non-opioid. If this does not relieve the pain, an opioid for mild to moderate pain should be added. When an opioid for mild to moderate pain in combination with a non-opioid fails to relieve the pain, an opioid for moderate to severe pain should be substituted. Only one drug from each of the groups should be used at the same time. Adjuvant drugs should be given for specific indications. If a drug ceases to be effective, do not switch to an alternative drug of similar efficacy … but prescribe a drug that is definitely stronger."
    - For the individual – The right dose is the dose that relieves the patient's pain.
    - With attention to detail – The first and last doses of the day should be linked to the patient's waking time and bedtime. Ideally, the patient's analgesic medication regimen should be written out in full for the patient and their family to work from.
- Previous guidelines recommend that dose takes into account the associated development of tolerance and possible development of physical dependence. Tolerance is characterized by decreased efficacy and duration of action of the opioid medication with repeated administration, requiring an increased dose to maintain the analgesic effect. It states that in practice, physical dependence and tolerance do not prevent the effective use of these medications. Patients with stable disease often remain on a stable dose for weeks or months. Previous guidelines discount the development of psychological dependence in cancer patients as a result of receiving opioids for relief of pain. The guidelines also recommend that the regimen offered accounts for disease-induced alterations in opioid pharmacokinetics, especially in cirrhosis and renal failure. If a patient appears to be intolerant to morphine, an alternative strong opioid is recommended.
- Choice of analgesic – The array of specific non-opioids considered included acetylsalicylic acid (ASA) 500-600mg every 4-6 hours, other NSAIDs (such as those on essential medicines lists, e.g. ibuprofen 400mg every 4-6 hours and ~~indometacin~~indomethacin 25mg every 6 hours), and paracetamol 650-1000mg every 4-6 hours. Specific choice from this selection "will depend on factors such as local availability and cost." The guidelines take note of typical contraindications such as gastric irritation, toxicities, hypersensitivity reactions, and other potential adverse effects of these medications, and notes the maximum dosages for each of the medications to avoid excess adverse effects: maximum 4g of ASA per day, maximum 6g paracetamol per day, maximum 3g ibuprofen per day, maximum 200mg ~~indometacin~~indomethacin per day.

  The 1996 guidelines state that the initial dose of an opioid for moderate to severe pain depends mainly on the patient's previous medication. For those who have previously received 60-100mg of codeine by mouth, they state that a starting dose of 10-15mg of morphine is usually adequate. Dose should be halved if the patient becomes somnolent after the first dose and is free of pain. If after 24 hours on this medication,

Not all medications were discussed with regards the maintenance of pain management. Dosages for medications should be increased according to clinical assessment. The recommended starting regimens for each medication discussed are:

- Codeine by mouth 30-120mg every four hours.
- Morphine by simple aqueous solution or tablet every four hours, or by slow release tablets every 12 hours. The correct dose is "the dose that works" to relieve a patient's pain. Typical starting dose 10-15mg.
- Standardised opium – no standard dose given.
- Tramadol usual dose by mouth 50-100mg every 4-6 hours.
- Hydromorphone usual starting dose 1-2mg by mouth or 1mg by subcutaneous injection, analgesia lasting 3-4 hours. Doses of hydromorphone by injection are typically 1/3 to ½ of the previously satisfactory oral dose.
- Methadone 5-10mg by mouth or by subcutaneous injection, analgesia lasting 6-12 hours.
- Levorphanol usual starting dose 1-2mg by mouth four times per day. Half dose for injection.
- Pethidine 50-100mg may be given every three hours as a starting dose, or more frequently in patients with severe cancer pain.
- Oxycodone usual starting dose 5-15mg by mouth or rectally, analgesia lasting 3-5 hours.
- Buprenorphine dose to account for its 60 times greater potency than orally administered morphine. When pain is no longer controlled by buprenorphine, 100 times the previously administered total daily dose of buprenorphine should be given of oral morphine sulfate in a four hourly regimen instead. It states that most patients' pain is satisfactorily controlled on an 8 hour regimen.

- Night doses – medications should be given through the night or in a larger dose at bedtime to sustain the plasma level of the medication within the effective range. Many patients with a double dose of morphine do not need a further dose until morning. A double dose is not necessary with slow release preparations of morphine or with longer0acting medications such as methadone and buprenorphine.

New (draft) recommendation:
In adults (including the older person) and adolescents with pain related to active cancer, any opioid may be considered for maintenance of pain relief, depending on clinical assessment and pain severity, in order to achieve rapid, effective and safe pain control
(Strong recommendation; low quality)

The choice of analgesic medication, dosage, and timing should take into the specific pharmacokinetics of each opioid medication, their contraindications, and their adverse effects in different patients.

Strength of Recommendation	**Strong**

Quality of Evidence	➢ **Low (Mixed)** [Pain (critical) = moderate to high for combination high-potency opioid + NSAID. Low to moderate for other scattered comparisons. See network meta analysis for further delineation of the quality of evidence for this outcome. Pain reduction maintenance (critical) = low Pain relief maintenance (critical) = low Pain relief speed (important) = low Functional outcomes (important) = low Sedation (important) = very low others omitted for no or indeterminate data]
Justification	The quality of the RCT evidence concerning the use of one of the analgesics studied over others was mixed – high for some comparisons and moderate, low, or very low for other comparisons. Across the many trials and comparisons, the GDG felt that there was no obviously-best treatment for maintenance of pain relief. The choice of opioid therefore largely depends on factors such as clinical assessment, cost, and patient preference. The GDG felt that a strong recommendation was warranted due to the strength of informed medical consensus on the administration of appropriate-strength analgesics to patients who need them. To suggest uncertainty in this regard risks undermining the strong case that low-resource settings would often achieve better coverage of adequate services by choosing cheaper options instead of the more expensive options frequently sold to them. It could also risk exacerbating widespread misconceptions on whether to use strong opioid analgesics or not. Furthermore, the GDG felt strongly that a range of weak and strong analgesic medications should be available to adult, adolescent, and older persons with cancer pain since there is variation in individuals' responses to specific analgesic medications, and wanted to be clear with a strong recommendation that having only a small selection was inadequate for appropriate treatment of mild, moderate, and severe pain. The GDG also saw this question as an opportunity to clarify that patients should be started on an analgesic that is appropriate to their level of pain, which was not clear from the 1996 guidelines which led to a common belief that patients should be started only on the first step of the cancer pain analgesic ladder, i.e. a non-opioid +/- adjuvant. It was felt that a conditional recommendation would not be clear enough that this practice is harmful and should be amended.
Subgroup considerations	
Implementation considerations [incl. M&E]	
Research priorities	

1.3. In adults (including older persons) and adolescents with pain related to active cancer receiving first-line treatment with opioids for background pain, what is the most effective opioid treatment for breakthrough pain?

One randomized controlled trial compared analgesics specifically for management of breakthrough pain. It was conducted in a population of older persons with varied cancer types.[20]

The trial provided low strength of evidence that the choice between sustained-release and immediate-release morphine may make no difference to prevent breakthrough pain (OR 1.00; 95% CI 0.75, 1.33) or to reduce pain (summary difference on a 0 to 100 [best] scale = -0.2; 95% CI -1.0,0.6).

No trial reported on pain relief speed, pain relief maintenance, quality of life, functional outcomes, or respiratory depression.

The trial provided very low strength of evidence, regarding differences between sustained-release and immediate-release morphine to avoid confusion. In the cross-over study, two patients developed confusion while taking immediate-release morphine, but the confusion was not attributed to the opioids.

Evidence Profile 1.3. Treatment of Breakthrough Pain

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Immediate-Release Morphine**	**Sustained-Release Morphine**	**Relative (95% CI)**	**Absolute (95% CI)**		
Pain relief (categorical) (follow-up: 6 days)												
1 [1]	RCT	not serious	N/A	not serious	serious [A]	single study	25/34 (74%)	25/34 (74%)	**RR 1.00** (0.75, 1.33)	**0 more per 1000** (from 210 fewer to 210 more)	Low	CRITICAL
Pain relief (continuous) (follow up: 6 days; assessed with VAS 0-100 [worst] [B])												
1 [1]	RCT	not serious	N/A	not serious	serious [A]	single study	34	34	**Diff -0.2** (-1.0, 0.6)		Very Low	CRITICAL
Pain relief speed												
0									not estimable		-	CRITICAL
Pain reduction maintenance												
0									not estimable		-	CRITICAL
Quality of life												
0									not estimable		-	CRITICAL
Functional outcomes												
0									not estimable		-	CRITICAL
Adverse events: Respiratory depression												
0 [B]									not estimable			IMPORTANT
Adverse events: Confusion												
1 [1]	RCT	not serious	N/A	not serious	very serious [C]	single study	2/34 (6%) [D]	0/34 (0%)	**RR 5.00** (0.25, 100)	**57 more per 1000** (from 37 fewer to 151 more)		IMPORTANT

Abbreviations: CI: *Confidence interval;* ***Diff:*** *difference (between groups);* ***IV:*** *intravenous;* ***NS****: not statistically significant;* ***RCT:*** *randomized controlled trial(s);* ***SQ****: subcutaneous.*

Explanations

A. Small study.
B. Scales transformed to 0 to 100, as necessary.

C. Small study with wide confidence interval.
D. Not attributed to morphine.

Trials

1. Finn, J. W., Walsh, T. D., MacDonald, N., Bruera, E., Krebs, L. U., Shepard, K. V. Placebo-blinded study of morphine sulfate sustained-release tablets and immediate-release morphine sulfate solution in outpatients with chronic pain due to advanced cancer. J Clin Oncol; May 1993.

<table>
<tr><td colspan="3">Evidence-to-Decision table 1.3</td></tr>
<tr><td colspan="3">In adults (including older persons) and adolescents with pain related to active cancer receiving first-line treatment with opioids for background pain, what is the most effective opioid treatment for breakthrough pain?</td></tr>
<tr><td>POPULATION:</td><td>Adults (including older persons) and adolescents with cancer-related pain</td><td rowspan="7">Background:

Cancer was responsible for 8.8 million deaths in 2015[7]. The prevalence of breakthrough pain in adult populations with cancer is reported to be almost 60%[53].

Current WHO recommendation:
In addition to normal doses in a regiment of analgesics given for cancer pain relief, rescue doses for incident (intermittent) and breakthrough pain should be given that are 50-100% of the regular four hourly dose.</td></tr>
<tr><td>INTERVENTION:</td><td>Opioids</td></tr>
<tr><td>COMPARISON:</td><td>Other opioids</td></tr>
<tr><td>MAIN OUTCOMES:</td><td>• Pain relief
• Pain relief speed
• Pain relief maintenance
• Quality of life (QoL)
• Functional outcomes
• Respiratory depression (adverse event)
• Confusion (adverse event)</td></tr>
<tr><td>STRATIFICATIONS:</td><td>• Age (adults, older persons, adolescents, children)
• History of substance abuse
• Refractory pain</td></tr>
<tr><td>SETTING:</td><td>All</td></tr>
<tr><td>PERSPECTIVE:</td><td>Population</td></tr>
</table>

	CRITERIA	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** Yes	Cancer was responsible for 8.8 million deaths in 2015[7]. Expert opinion and data from country experiences from several low-income countries suggest that approximately 80% of people dying from cancer experience moderate or severe pain lasting on average 90 days[6]. A recent systematic review of published evidence reports a similarly high figure that 66.4% of patients with advanced, metastatic, or terminal disease experience pain[52]. The prevalence of breakthrough pain in adult populations with cancer is reported to be almost 60%[53].

BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Yes: ☐ No: ☐ Uncertain: Yes	• **One randomized controlled trial** compared analgesics specifically for management of breakthrough pain. It was conducted in a population of older persons varied cancer types. Studies that only compared a medication with placebo were excluded. **BENEFITS and HARMS** • **One trial** provided **low strength of evidence** that the choice between **sustained-release and immediate-release morphine may make no difference to prevent breakthrough pain** (RR 1.00; 95% CI 0.75, 1.33) or to **reduce pain** (summary difference on a 0 to 100 [best] scale = -0.2; 95% CI -1.0, 0.6). • **No trial** reported on **pain relief speed**. • **No trial** reported on **pain relief maintenance**. • **No trial** reported on **QoL**. • **No trial** reported on **functional outcomes**. • **No trial** reported on **respiratory depression.** • Based on **one trial** that provided **very low strength of evidence**, we are uncertain about differences between **sustained-release and immediate-release morphine** to avoid **confusion.** **STRATIFICATIONS** • Studies conducted in adults with a wide age range, without stratification into adolescent, non-older persons, and older persons. • Studies provide no data regarding history of substance abuse. • Studies provide no data regarading refractory pain. **SUMMARY** There may be no difference in likelihood of breakthrough pain or overall pain relief between sustained-release and immediate-release morphine.

ACCEPTABILITY & PREFERENCES	**Is there important uncertainty or variability about how much people value the options?** Major variability [ ] Minor variability [ ] Uncertain [Yes] **Is the option acceptable to key stakeholders?** Yes [ ] No [ ] Uncertain [Yes]	**Research Evidence** None **Additional considerations** None

FEASIBILITY ./ RESOURCE USE

How large are the resource requirements?

Major ☐ Minor ☐ Uncertai Yes

Is the option feasible to implement?

Yes ☐ No ☐ Uncertain Yes

Source:[12]	Number of Countries Where Available for Free	Number of Countries Where Available	Price of one 30-Day Opioid Treatment			
			Median	IQR	Mean	SD
Morphine oral immediate release (tablet, capsule)	11	35	$ 49.70	$ 80.50	$ 78.50	$ 92.00
Morphine oral slow release (tablet, capsule)	15	44	$ 56.80	$ 110.50	$ 83.80	$ 90.70
Morphine oral (liquid)	9	26	$ 41.90	$ 96.50	$ 67.58	$ 63.60
Morphine injectable (ampoule)	19	49	$ 88.50	$ 167.30	$ 167.20	$ 225.30
Fentanyl (transdermal patch)	15	47	$ 81.20	$ 263.40	$ 144.60	$ 154.10
Methadone oral solid (tablet, capsule)	9	22	$ 26.50	$ 38.30	$ 40.50	$ 29.10
Methadone oral (liquid)	9	26	$ 13.10	$ 70.90	$ 58.80	$ 103.40
Oxycodone oral immediate release (tablet, capsule)	6	19	$ 202.90	$ 156.80	$ 198.10	$ 125.20
Oxycodone oral slow release (tablet, capsule)	6	21	$ 237.20	$ 473.70	$ 312.40	$ 252.10
Hydromorphone oral immediate release (tablet, capsule)	2	7	$ 103.45	$ 115.60	$ 78.30	$ 61.50
Hydromorphone oral slow release (tablet, capsule)	3	10	$ 14.97	$ 89.10	$ 51.60	$ 54.90
Hydromorphone oral (liquid)	0	2	$ 146.20	NA	$ 150.30	$ 146.20
Hydromorphone injectable (ampoule)	2	4	$ 101.10	NA	$ 73.20	$ 101.10

Additional considerations

		The GDG noted that while no recommendation would be made for this PICO (instead a best practice statement would be made), it was worth highlighting that the cost of certain formulations, such as sublingual fentanyl, were likely to be prohibitively expensive for some low- and middle-income settings.
	Would the option improve equity in health? Yes ☐ No ☐ Uncertai Yes	**Research Evidence** None **Additional considerations** None

Recommendation	**Current recommendation:** In addition to normal doses in a regiment of analgesics given for cancer pain relief, rescue doses for incident (intermittent) and breakthrough pain should be given that are 50-100% of the regular four hourly dose. **New (draft) recommendation:** None.
Strength of Recommendation	
Quality of Evidence	➢ **Low** [Pain (critical) = low (one medication comparison) others omitted for no or inconclusive data]
Justification	The GDG felt that they could not justify making a recommendation on the basis of only one eligible low quality RCT that looked at too few of the options available clinically. The task of systematically reviewing the question was also confounded by differing definitions of breakthrough pain across trials. The GDG opted instead for a best practice statement on the matter because the GDG felt that, in the interests of patients, WHO should not remain silent on the issue.
Subgroup considerations	
Implementation considerations [incl. M&E]	
Research priorities	

Key Question 2: Opioid Rotation/Switching

2.1. In adults (including older persons) and adolescents with pain related to active cancer and who are taking a single opioid, what is the evidence for the practice of opioid rotation or opioid switching as compared with continuing use of one opioid in order to maintain effective and safe pain control and minimize adverse effects?

No eligible studies were found that address this Key Question.

Evidence-to-Decision table 2.1		
In adults (including older persons) and adolescents with pain related to active cancer and who are taking a single opioid, what is the evidence for the practice of opioid rotation or opioid switching as compared to continuing use of one opioid in order to maintain effective and safe pain control and minimize adverse effects?		
POPULATION:	Adults (including older persons) and adolescents with cancer-related pain	**Background:** Patients with cancer pain may not respond to increasing doses of opioids because they develop adverse effects before achieving an acceptable level of analgesia, or the analgesic response is poor, despite a rapid dose escalation. It is supposed that opioid switching might improve the balance between analgesia and adverse effects[54]. There was interest from the GDG and historical external interest that the practice be considered in the guidelines under development (e.g. [55]). **Current WHO recommendation**: None.
INTERVENTION:	Opioid rotation or switching	
COMPARISON:	Continued use of one opioid	
MAIN OUTCOMES:	• Pain relief • Pain relief speed • Pain relief maintenance • Quality of life (QoL) • Functional outcomes • Sedation (adverse event) • Respiratory depression (adverse event)	
STRATIFICATIONS:	• Age (adults, older persons, adolescents, children) • History of substance abuse • Refractory pain	
SETTING:	All	
PERSPECTIVE:	Population	

	CRITERIA	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	Opioid switching is a common practice that gained prominence since the publication of the 1996 WHO cancer pain guidelines. If possible, WHO should provide evidence-based global guidance on this common where none hitherto exists.

BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Yes: [ ] No: [ ] Uncertain: [Yes]	• **No randomized controlled trials** **BENEFITS and HARMS** • **No trial** reported on **pain relief**. • **No trial** reported on **pain relief speed**. • **No trial** reported on **pain relief maintenance**. • **No trial** reported on **QoL**. • **No trial** reported on **functional outcomes**. • **No trial** reported on **sedation**. • **No trial** reported on **respiratory depression**. **STRATIFICATIONS** • Studies conducted in adults with a wide age range, without stratification into adolescent, non-older persons, and older persons. • Studies provide no data regarding history of substance abuse. • Studies provide no data regarading refractory pain. **SUMMARY** No eligible trials were found that address this sub-question.

ACCEPTABILITY & PREFERENCES	**Is there important uncertainty or variability about how much people value the options?** Major variability [ ] Minor variability [ ] Uncertain [Yes] **Is the option acceptable to key stakeholders?** Yes [ ] No [ ] Uncertain [Yes]	**<u>Research Evidence</u>** None **<u>Additional considerations</u>** None

FEASIBILITY ./ RESOURCE USE

How large are the resource requirements?

Major ☐ Minor ☐ Uncertai Yes

Is the option feasible to implement?

Yes ☐ No ☐ Uncertain Yes

Source:[12]	Number of Countries Where Available for Free	Number of Countries Where Available	Price of one 30-Day Opioid Treatment			
			Median	IQR	Mean	SD
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Hydromorphone injectable (ampoule)	2	4	$ 101.10	NA	$ 73.20	$ 101.10

Additional considerations

		None
	Would the option improve equity in health? Yes No Uncertai Yes	**<u>Research Evidence</u>** None **<u>Additional considerations</u>** None

Recommendation	**Current recommendation:** None **New (draft) recommendation:** None
Strength of Recommendation	
Quality of Evidence	
Justification	The GDG could not make a new recommendation in the absence of evidence.
Subgroup considerations	
Implementation considerations [incl. M&E]	
Research priorities	The GDG believed there were few studies on this subject potentially due to ethical restrictions.

Key Question 3: Opioid Formulation

3.1. In adults (including older persons) and adolescents with pain related to active cancer, what is the evidence for the benefit of administering modified release morphine regularly as compared with immediate release morphine on a 4-hourly or as required basis, in order to maintain effective and safe pain control?

Ten eligible RCTs compared modified-release morphine (morphine SR) versus immediate-release morphine (morphine IR, see Evidence Profile 3.1).[15,20,27,56-63] These trials generally included all patients with cancer pain. Within studies, participants had either a variety of types of cancer (e.g., breast, prostate, colon, lung, lymphatic, gastric, liver) or the studies did not report cancer types (implying a variety of cancers. Study participants generally had moderate or severe pain (or the level of pain severity was not explicitly described). Among studies that reported participant ages, study participants were generally middle-age to older adults (mostly about 40 or 50 to 70 or 90 years old).

The trials evaluated a variety of formulations of morphine SR (MS Contin®, Oramorph SR®, Skenan®, MST Continus®, Kapanol®, or vague or not described specific formulations). None of the trials used combined morphine SR and scheduled doses of morphine IR. Among studies that described management of breakthrough pain, all allowed similar treatment in both study arms (morphine SR or morphine IR). One trial used ketobemidone for breakthrough pain; the others used morphine IR. All studies (at least implicitly) prescribed the morphine IR to be taken on a fixed schedule. Half the trials did not report on the use of other analgesics or adjuvant treatments. Two trials reported that patients were allowed to continue but not change their other treatments; two trials explicitly allowed only either acetaminophen or NSAIDs. Only one trial mandated concomitant therapy: diclofenac (a NSAID) and haloperidol (used as an antiemetic).

In brief, there is moderate strength of evidence of no difference in pain relief between modified- and immediate-release morphine. Three of four trials found 100% pain-relief regardless of which modality was used (moderate strength of evidence). Pooling all four studies yielded a summary RR = 0.99 (95% CI 0.95, 1.03). Four trials found similar pain scores (see Forest Plot 3.1 below) among participants on either treatment (moderate strength of evidence). The summary difference in pain scores (transformed to a 0 to 100 [worst]) scale) was -0.6 (95% CI -5.9, 4.8).

One small trial provided low strength of evidence of no difference in pain relief speed (time to achieving stable pain control, difference between arms -0.4 days; 95% CI -1.1, 0.3). The same trial provided very low strength of evidence of no difference for quality of life, with a difference between arms of 9 points (on a transformed scale of 1 to 100 [best]) with 95% CI -6 to 24.

No eligible studies evaluated pain reduction maintenance or functional outcomes. Two studies provided low strength of evidence regarding sedation. Neither study evaluated the outcome as an adverse event, but rather on a scale. The two studies found no differences in sedation scores (on a 0 to 100 [worst]). Combined, the difference was -2.9 (95% CI -14.2, 8.5). Only two trials explicitly reported on respiratory depression as a

potential adverse event. They provided low strength of evidence finding no events in a small overall sample of patients. None of the RCTs evaluated subgroups of interest (adult/older adult/adolescent, history of substance abuse, refractory pain). Only a single study was restricted to "adults" (31-62 years old)[58] and one study to "older adults" (57-71 years old),[63] precluding meaningful across-study comparison of these age groups. Although, not explicitly clear based on study eligibility criteria, it is likely that very few if any study participants had a history of substance abuse or refractory pain.

Evidence Profile 3.1. Modified-Release vs. Immediate-Release Morphine

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Modified Release Morphine**	**Immediate Release Morphine**	**Relative (95% CI)**	**Absolute (95% CI)**		
Pain relief (categorical) (follow up: range 6 days to 14 days; assessed with VAS 0-100 [worst] [A])												
4 [1,2,3,4]	RCT	serious [B]	not serious	not serious	not serious	none	108/111 (97.3%)	111/111 (100%)	**RR 0.99** (0.95, 1.03)	**27 more per 1000** (from 60 fewer to 4 more)	Moderate	CRITICAL
Pain relief (continuous) (follow up: range 24 hours to 14 days; assessed with VAS, PPI 0-100 [worst] [A])												
4 [5,6,7,8]	RCT	not serious	not serious	not serious	serious [C]	none	77	73	**Diff --0.6** (-5.9, 4.8)		Moderate	CRITICAL
Pain relief speed (achievement of stable pain control, follow up: 6 days)												
1 [6]	RCT	not serious	N/A	not serious	serious [C]	single study	19	15	**Diff -0.4 days** (-1.1, 0.3)		Low	IMPORTANT
Pain reduction maintenance												
0									not estimable			CRITICAL
Quality of life (follow up: 8 days; assessed with: EORTC; Scale: 0 to 100 [best])												
1 [6]	RCT	not serious	N/A	serious [D]	serious [C]	single study	19	15	**Diff 9** (-6, 24)		Very Low	CRITICAL
Functional outcomes												
0									not estimable			CRITICAL
Adverse events: Sedation (follow up: range 2 days to 14 days; assessed with VAS 0-100 [worst] [A])												
2 [4,9]	RCT	not serious	not serious	serious [E]	serious [C]	none	62	62	**Diff 2.9** (-14.2, 8.5)		Low	IMPORTANT
Adverse events: Respiratory depression (follow up: range 2 days to 14 days)												
2 [4,10]	RCT	not serious	not serious	not serious	very serious [F]	no events	0/63 (0%)	0/63 (0%)	not estimable		Low	IMPORTANT

Abbreviations: ***CI***: *confidence interval;* ***CR***: *controlled release;* ***Diff***: *difference (between groups);* ***EORTC***: *European Organisation for Research and Treatment of Cancer;* ***IR***: *immediate release;* ***N/A***: *not applicable;* ***NS***: *not statistically significant;* ***PPI***: *Present Pain Intensity;* ***RCT***: *Randomized controlled trial(s);* ***RR***: *Relative Risk (log scale);* ***VAS:*** *Visual Analog Scale.*

Explanations

A. Scales transformed to 0 to 100, as necessary.

B. Serious limitations related to lack of blinding and high attrition.
C. Small sample size (and/or wide confidence interval).
D. EORTC is a measure of quality of life that mixes concepts of both quality of life and functional outcomes.
E. Not reporting of adverse event rates, per se, but sedation measured on scales.
F. Small sample size and relative effect not estimable.

Trials

1. Ventafridda, V., Saita, L., Barletta, L., Sbanotto, A., De Conno, F. Clinical observations on controlled-release morphine in cancer pain. J Pain Symptom Manage; Sep 1989.
2. Knudsen, J., Mortensen, S. M., Eikard, B., Henriksen, H. [Morphine depot tablets compared with conventional morphine tablets in the treatment of cancer pain]. Ugeskr Laeger; Feb 25 1985.
3. Gillette, J. F. Ferme,C., Moisy, N, et al. Double-blind crossover clinical and pharmacokinetic comparison of oral morphine syrup and sustained release morphine sulfate capsules in patients with cancer-related pain. Clinical Drug Investigation; 1997.
4. Finn, J. W., Walsh, T. D., MacDonald, N., Bruera, E., Krebs, L. U., Shepard, K. V. Placebo-blinded study of morphine sulfate sustained-release tablets and immediate-release morphine sulfate solution in outpatients with chronic pain due to advanced cancer. J Clin Oncol; May 1993.
5. Thirlwell, M. P., Sloan, P. A., Maroun, J. A., et al. Pharmacokinetics and clinical efficacy of oral morphine solution and controlled-release morphine tablets in cancer patients. Cancer; Jun 01 1989.
6. Klepstad, P., Kaasa, S., Jystad, A., Hval, B., Borchgrevink, P. C. Immediate- or sustained-release morphine for dose finding during start of morphine to cancer patients: a randomized, double-blind trial. Pain; Jan 2003.
7. Hanks, G. W., Twycross, R. G., Bliss, J. M. Controlled release morphine tablets: a double-blind trial in patients with advanced cancer. Anaesthesia; Aug 1987.
8. Arkinstall, W. W., Goughnour, B. R., White, J. A., Stewart, J. H. Control of severe pain with sustained-release morphine tablets v. oral morphine solution. Cmaj; Mar 15 1989.
9. Walsh, T. D. Clinical evaluation of slow release morphine tablets. Advances in Pain Research and Therapy; 1985.
10. Cundiff, D., McCarthy, K., Savarese, J. J., et al. Evaluation of a cancer pain model for the testing of long-acting analgesics. The effect of MS Contin in a double-blind, randomized crossover design. Cancer; Jun 01 1989.

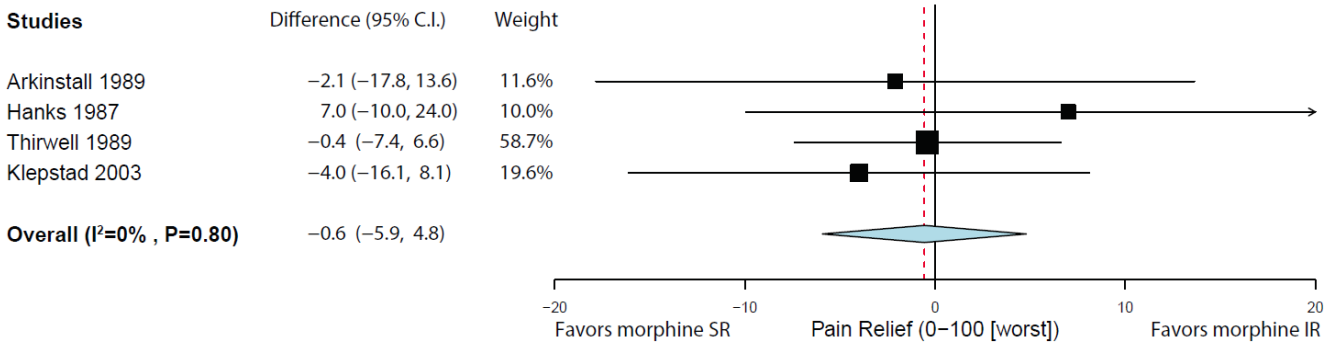
Evidence-to-Decision table 3.1		
In adults (including older persons) and adolescents with pain related to active cancer, what is the evidence for the benefit of administering modified release morphine regularly as compared to immediate release morphine on a 4-hourly or as required basis, in order to maintain effective and safe pain control?		
POPULATION:	Adults (including older persons) and adolescents with cancer-related pain	**Background:** Clinical staff and patients are often faced with the options of administering modified-release morphine regularly or immediate-release morphine on a 4-hourly basis. There is some debate as to the importance of the differences between the medications[64,65] **Current WHO recommendation**: The 1996 WHO Guidelines discuss the options of a 4-hourly regimen of morphine or slow-release morphine tablets every 12 hours. "The correct dose is the dose that works", though it states that in most patients, pain is controlled with 10-30mg every four hours. Slow release morphine tablets vary in strength between 10mg to 200mg. The analgesic should be given at regular time intervals, not merely when the patient complains of pain. The use of morphine should be dictated by intensity of pain, not by life expectancy.
INTERVENTION:	Modified release morphine	
COMPARISON:	Immediate release morphine	
MAIN OUTCOMES:	• Pain relief • Pain relief speed • Pain relief maintenance • Quality of life (QoL) • Functional outcomes • Sedation (adverse event) • Respiratory depression (adverse event)	
STRATIFICATIONS:	• Age (adults, older persons, adolescents, children) • History of substance abuse • Refractory pain	
SETTING:	All	
PERSPECTIVE:	Population	

	CRITERIA	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	**Research Evidence** Global consumption of morphine in 2015 was 39.6 tonnes[66]. Both immediate release and modified/extended/slow-release formulations are commonly used in clinical practice. Yet there is some debate as to the importance of the differences between the medications[64,65]. **Additional considerations** WHO should, if possible, provide evidence based guidance on the matter.

BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Yes: ☐ No: ☐ Uncertain: ☒ Yes	• **Ten randomized controlled trials** compared modified-release versus immediate-release morphine. The trials generally included all patients with cancer pain. Within trials, participants had either a variety of types of cancer (e.g., breast, prostate, colon, lung, lymphatic, gastric, liver) or the trials did not report cancer types (implying a variety of cancers). Among trials that reported participant ages, trial participants were generally middle-age to older adults (mostly about 40 or 50 to 70 or 90 years old). In all trials, patients being given modified-release morphine were also being offered immediate release morphine as a rescue medication. Therefore, strictly speaking, the comparison is between modified-release morphine with immediate release morphine as rescue mediation compared with immediate-release morphine as maintenance and rescue medication. **BENEFITS and HARMS** • **Four trials** provided **moderate strength of evidence** of **no difference in pain relief between modified- and immediate-release morphine**. Four trials mostly found 100% pain-relief regardless of which modality was used (moderate strength of evidence), yielding a summary RR = 0.99 (95% CI 0.95, 1.03). **Four trials** provided **moderate strength of evidence** of no difference in pain scores. Summary difference in pain scores (transformed to a 0 to 100 [worst]) scale) was -0.6 (95% CI -5.9, 4.8). • **One trial** provided **low strength of evidence** of **no difference in pain relief speed** (difference between arms -0.4 days; 95% CI -1.1, 0.3). • **One trial** provided **very low strength of evidence** regarding **modified-release morphine for improved QoL**, with a difference between arms of 9 points (on a transformed scale of 1 to 100 [best]) with 95% CI -6 to 24**.** We are uncertain of any difference. • **No trial** reported on **functional outcomes**. • **Two trials** provided **low strength of evidence** of **no difference in sedation.** Neither trial evaluated the outcome as an adverse event, but rather on a scale. The difference in sedation scores (on a 0 to 100 [worst] was 2.9 (95% CI -14.2, 8.5)**.** • **Two trials** provided **low strength of evidence** with **no respiratory distress events in a small sample of patients.** **STRATIFICATIONS** • Studies conducted in adults with a wide age range, without stratification into adolescent, non-older persons, and older persons. • Studies provide no data regarding history of substance abuse. • Studies provide no data regarading refractory pain. **SUMMARY**

The choice of modified-release and immediate-release morphine probably makes little or no difference to pain relief and may make no difference to pain relief speed, maintenance of pain relief, and sedation. Respiratory distress events may be rare with both formulations.

Forest Plot 3.1. Pain Relief (Continuous Scale) Modified-Release vs. Immediate-Release Morphine



***Abbreviation**: **CI**: confidence interval.*

Scores from individual studies have been transformed to a uniform 0-100 scale (100 = worst).

ACCEPTABILITY & PREFERENCES	**Is there important uncertainty or variability about how much people value the options?** Major variability Yes Minor variability Uncertain **Is the option acceptable to key stakeholders?** Yes No Uncertain Yes	**<u>Research Evidence</u>** None **<u>Additional considerations</u>** The GDG identified reasons for variability in patient preferences from clinical experience. Some patients prefer modified release morphine because of the lower pill burden, more even analgesia, and less waking at night. Other patients, however, may prefer a higher pill burden for psychological reasons. In other patients still there may be stigma against certain formulations. This indicates major variability. The GDG deemed variability in clinicians preferences between the two formulations to be minor, considering there to be no strong reasons for a clinician or other key stakeholder to prefer one over the other.

FEASIBILITY ./ RESOURCE USE

How large are the resource requirements?

Major	Minor	Uncertai
	Yes	

Is the option feasible to implement?

Yes	No	Uncertain
Yes		

Research Evidence

Source:[12]	Number of Countries Where Available for Free	Number of Countries Where Available	Price of one 30-Day Opioid Treatment			
			Median	**IQR**	**Mean**	**SD**
Morphine oral immediate release (tablet, capsule)	11	35	$ 49.70	$ 80.50	$ 78.50	$ 92.00
Morphine oral slow release (tablet, capsule)	15	44	$ 56.80	$ 110.50	$ 83.80	$ 90.70
Morphine oral (liquid)	9	26	$ 41.90	$ 96.50	$ 67.58	$ 63.60
Morphine injectable (ampoule)	19	49	$ 88.50	$ 167.30	$ 167.20	$ 225.30
Fentanyl (transdermal patch)	15	47	$ 81.20	$ 263.40	$ 144.60	$ 154.10
Methadone oral solid (tablet, capsule)	9	22	$ 26.50	$ 38.30	$ 40.50	$ 29.10
Methadone oral (liquid)	9	26	$ 13.10	$ 70.90	$ 58.80	$ 103.40
Oxycodone oral immediate release (tablet, capsule)	6	19	$ 202.90	$ 156.80	$ 198.10	$ 125.20
Oxycodone oral slow release (tablet, capsule)	6	21	$ 237.20	$ 473.70	$ 312.40	$ 252.10
Hydromorphone oral immediate release (tablet, capsule)	2	7	$ 103.45	$ 115.60	$ 78.30	$ 61.50
Hydromorphone oral slow release (tablet, capsule)	3	10	$ 14.97	$ 89.10	$ 51.60	$ 54.90
Hydromorphone oral (liquid)	0	2	$ 146.20	NA	$ 150.30	$ 146.20
Hydromorphone injectable (ampoule)	2	4	$ 101.10	NA	$ 73.20	$ 101.10

		Additional considerations Typically, modified release formulations are more expensive per dose. It is not clear which formulation is more cost effective.
	Would the option improve equity in health? Yes No Uncertai Yes ☐ ☐	**Research Evidence** None **Additional considerations** Modified release morphine is typically more expensive and its use probably makes little to no difference to pain relief, pain relief speed, maintenance of pain relief, and sedation. The GDG noted the problem that in many settings, especially some low income ones, only modified release morphine is available where a faster release morphine is necessary for breakthrough pain relief. They reported that in some settings, clinical staff are forced to crush up modified release medication in order to make it release more quickly, since immediate release morphine is not available. On occasion, injectable immediate release morphine is available, but this is less appropriate for outpatients. Ensuring that both modified- and immediate-release morphine is available in an oral formulation would increase equity.

Recommendation	**Current recommendation:** The 1996 WHO Guidelines discuss the options of a 4-hourly regimen of morphine or slow-release morphine tablets every 12 hours. "The correct dose is the dose that works", though it states that in most patients, pain is controlled with 10-30mg every four hours. Slow release morphine tablets vary in strength between 10mg to 200mg. The analgesic should be given at regular time intervals, not merely when the patient complains of pain. The use of morphine should be dictated by intensity of pain, not by life expectancy. N**ew (draft) recommendation:** Regularly-dosed immediate-release oral morphine, or regularly-dosed slow-release morphine should be used for pain relief. With either formulation, immediate-release oral morphine should be used as rescue medication.
Strength of Recommendation	**Strong**
Quality of Evidence	➢ **MODERATE** [Pain (critical) = moderate (pain relief), low (pain score) Pain relief speed (important) = low Pain reduction maintenance (critical) = low Sedation (adverse event) (important) = low Other outcomes omitted for no data or inconclusive findings]
Justification	Modified release morphine is typically more expensive and its use probably makes little to no difference to pain relief, pain relief speed, maintenance of pain relief, and sedation. Yet patients sometimes place high option value on the availability of both formulations. The GDG therefore felt that having both modified- and immediate-release morphine available in an oral formulation would be preferred, and either regimen (modified-release for pain relief maintenance with immediate release as rescue medication or immediate-release used for both) could be used. They noted that if a health system must choose between one or the other formulation, immediate-release oral morphine should be chosen as it can be used as both maintenance and rescue medication whereas modified release morphine cannot. The GDG complained that in many settings, especially some low- and middle-income ones, only modified release morphine is available, where a faster release morphine is necessary for breakthrough pain relief. They reported that in some settings, clinical staff are forced to crush up modified release medication in order to make it release more quickly, since immediate release morphine is not available. On occasion, injectable immediate release morphine is available, but this is less appropriate for outpatients.

	The text of the guidelines explains that the regularity of dosing should depend on clinical assessment and the recommendation applies only if the decision to use morphine has been made.
Subgroup considerations	
Implementation considerations [incl. M&E]	
Research priorities	

3.2. In adults (including older persons) and adolescents with pain related to active cancer, what is the evidence for the benefit of using the subcutaneous, transdermal, or transmucosal route as compared with the intramuscular and intravenous routes when the oral route for opioids is inappropriate (e.g. adults (including older persons) and adolescents with diminished consciousness, ineffective swallowing or vomiting) in order to maintain effective and safe pain control?

A single eligible study compared non-invasive routes versus injected routes for opioids (see Evidence Profile 3.2). The study was a crossover study of 20 adults with multiple types of cancer. Participants were chosen because they had had substantial side effects related to oral or rectal opioids. In brief, the study provided very low strength of evidence suggesting no difference in degree of pain relief with a difference between subcutaneous and intravenous hydromorphone (difference = 3.0; 95% CI -15, 21) on a 0 to 100 (worst) scale. The trial did not report on adverse events of interest, per se. The trial found that sedation, measured by VAS, improved in both arms with opioid treatment.

Evidence Profile 3.2. Subcutaneous vs. Intravenous Hydromorphone

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**SQ Opioid**	**IV Opioid**	**Relative (95% CI)**	**Absolute (95% CI)**		
Pain relief (categorical)												
0									not estimable		-	CRITICAL
Pain relief (continuous) (follow up: 2 days)												
1 [1]	RCT	not serious	N/A	not serious	very serious [A]	single study	20	20	**Diff 3.0** (-15.1, 21.1)		Very Low	CRITICAL
Pain relief speed												
0									not estimable		-	CRITICAL
Pain reduction maintenance												
0									not estimable		-	CRITICAL
Quality of life												
0									not estimable		-	CRITICAL
Functional outcomes												
0									not estimable		-	CRITICAL
Adverse events: Sedation												
0 [B]									not estimable			IMPORTANT
Adverse events: Toxicity												
0									not estimable			IMPORTANT

Abbreviations: CI: *Confidence interval;* ***Diff:*** *difference (between groups);* ***IV:*** *intravenous;* ***NS****: not statistically significant;* ***RCT:*** *randomized controlled trial(s);* ***SQ****: subcutaneous.*

Explanations

A. Small trial providing estimate with a wide confidence interval.
B. One study reported on sedation on a visual analog scale (Moulin 1991); however, sedation *improved* in both arms with opioid treatment.

Trials

1. Moulin, D. E., Kreeft, J. H., Murray-Parsons, N., Bouquillon, A. I.. Comparison of continuous subcutaneous and intravenous hydromorphone infusions for management of cancer pain. Lancet; Feb 23 1991.

Evidence-to-Decision table 3.2		
In adults (including older persons) and adolescents with pain related to active cancer, what is the evidence for the benefit of using the subcutaneous, transdermal, or transmucosal route as compared to the intramuscular and intravenous routes when the oral route for opioids is inappropriate (e.g. adults (including older persons) and adolescents with diminished consciousness, ineffective swallowing or vomiting) in order to maintain effective and safe pain control?		
POPULATION:	Adults (including older persons) and adolescents with cancer-related pain	**Background:** While the default preferred route for administration of opioid medications is the oral route, in some patients, this route may be inappropriate due to dysphagia or vomiting[67]. WHO has not issued evidence-based guidance on which alternative routes are preferred between subcutaneous, transdermal, or transmucosal routes compared with the intramuscular and intravenous routes. Yet these routes are commonly used in clinical practice. **Current WHO recommendation**: The 1996 WHO guidelines suggest that rectal, subcutaneous, intramuscular, spinal, or transdermal administration can be considered when the oral route is inappropriate, such as with dysphagia, common toward the end of life. The subcutaneous route should be considered if the patient is unable to take oral and rectal morphine. Repeated injections should be avoided, and continuous subcutaneous infusion is preferred. If injected, pethidine should be given intramuscularly because it causes tissue irritation. Intravenous injection of morphine can be either bolus injection or continuous infusion. The dose of morphine or other opioid is the same whether given subcutaneously, intramuscularly, or intravenously. In settings with the capacity for spinal administration, the epidural or intrathecal routes can be considered in patients who experience severe adverse effects or whose pain is poorly responsive to opioids. Transdermal fentanyl citrate is a proposed route of administration and it may have good patient compliance. But cost and availability might restrict its use in many settings.
INTERVENTION:	Subcutaneous, transdermal, or transmucosal opioid	
COMPARISON:	Intramuscular and intravenous opioid	
MAIN OUTCOMES:	• Effective cessation of opioid • Pain relief speed • Pain relief maintenance • Quality of life (QoL) • Functional outcomes • Sedation (adverse event) • Toxicity (adverse event)	
STRATIFICATIONS:	• Age (adults, older persons, adolescents, children) • History of substance abuse • Refractory pain	
SETTING:	All	
PERSPECTIVE:	Population	

	CRITERIA	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	**Research Evidence** While the default preferred route for administration of opioid medications is the oral route, in some patients, this route may be inappropriate in some patients due to diminished consciousness, ineffective swallowing, or vomiting[67]. **Additional considerations** WHO has not issued evidence-based guidance on which alternative routes are preferred between subcutaneous, transdermal, or transmucosal routes compared with the intramuscular and intravenous routes. Yet these routes are commonly used in clinical practice.

BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Yes: [ ] No: [ ] Uncertain: [Yes]	• **One randomized controlled trial** compared **subcutaneous vs. intravenous hydromorphone**. The study was conducted in adults with multiple types of cancer who could not tolerate oral or rectal opioids. **BENEFITS and HARMS** • **One trial** provided **very low strength of evidence** of **no difference in pain relief** between subcutaneous and intravenous hydromorphone.[68] • **No trial** reported on **pain relief speed**. • **No trial** reported on **pain relief maintenance**. • **No trial** reported on **QoL**. • **No trial** reported on **functional outcomes**. • **No trial** reported on **sedation**. (One trial found improved sedation with opioid treatments.) • **No trial** reported on **toxicity**. **STRATIFICATIONS** • Studies conducted in adults with a wide age range, without stratification into adolescent, non-older persons, and older persons. • Studies provide no data regarding history of substance abuse. • Studies provide no data regarading refractory pain. **SUMMARY** We are uncertain whether about relative effects between subcutaneous and intravenous hydromorphone.

ACCEPTABILITY & PREFERENCES	**Is there important uncertainty or variability about how much people value the options?** Major variability [ ] Minor variability [ ] Uncertain [Yes] **Is the option acceptable to key stakeholders?** Yes [ ] No [ ] Uncertain [Yes]	**<u>Research Evidence</u>** None **<u>Additional considerations</u>** None

FEASIBILITY ./ RESOURCE USE	**How large are the resource requirements?** Major ☐ Minor ☐ Uncertain ☒ Yes **Is the option feasible to implement?** Yes ☐ No ☐ Uncertain ☒ Yes	**<u>Research Evidence</u>** None **<u>Additional considerations</u>** None
	Would the option improve equity in health? Yes ☐ No ☐ Uncertain ☒ Yes	**<u>Research Evidence</u>** None **<u>Additional considerations</u>** None

Recommendation	**Current recommendation:** • The 1996 WHO guidelines suggest that rectal, subcutaneous, intramuscular, spinal, or transdermal administration can be considered when the oral route is inappropriate, such as with dysphagia, common toward the end of life. • The subcutaneous route should be considered if the patient is unable to take oral and rectal morphine. Repeated injections should be avoided, and continuous subcutaneous infusion is preferred. • If injected, pethidine should be given intramuscularly because it causes tissue irritation. • Intravenous injection of morphine can be either bolus injection or continuous infusion. • The dose of morphine or other opioid is the same whether given subcutaneously, intramuscularly, or intravenously. • In settings with the capacity for spinal administration, the epidural or intrathecal routes can be considered in patients who experience severe adverse effects or whose pain is poorly responsive to opioids. • Transdermal fentanyl citrate is a proposed route of administration and it may have good patient compliance. But cost and availability might restrict its use in many settings. **New (draft) recommendation:** None
Strength of Recommendation	**None**
Quality of Evidence	➢ Very Low [Pain relief (critical) = very low Other outcomes omitted for no data]
Justification	The GDG could not make a new recommendation on the basis of the low quality and amount of evidence.
Subgroup considerations	
Implementation considerations [incl. M&E]	
Research priorities	

Key Question 4: Opioid Cessation

4.1. In adults (including older persons) and adolescents with cancer-related pain, what is the evidence for certain dosing regimens or interventions in order to effectively and safely cease opioids?

No eligible studies were found that address this Key Question.

Evidence-to-Decision table 4.1		
In adults (including older persons) and adolescents with cancer-related pain, what is the evidence for certain dosing regimens or interventions in order to effectively and safely cease opioids?		
POPULATION:	Adults (including older persons) and adolescents with cancer-related pain	**Background:** Patients undergoing the cessation of opioids may experience withdrawal symptoms if they have developed physical dependence on opioids. How to cease opioids quickly and appropriately while avoiding withdrawal symptoms is an area of interest. **Current WHO recommendation**: If the cause of pain is addressed by anticancer treatment, the use of opioids can be stopped. To avoid withdrawal symptoms, the dose should be decreased gradually. After an abrupt reduction in pain (e.g. after nerve block or neuroablative procedure), the dose should be reduced to 25% of the original dose. If the procedure has been successful, the dose can be reduced further every 2-3 days and stopped completely if the pain does not recur.
INTERVENTION:	Opioid dosing regimen (for cessation)	
COMPARISON:	Other opioid dosing regimen	
MAIN OUTCOMES:	• Effective cessation of opioid • Pain relief speed • Pain relief maintenance • Quality of life (QoL) • Functional outcomes • Confusion (adverse event) • Gastrointestinal adverse event	
STRATIFICATIONS:	• Age (adults, older persons, adolescents, children) • History of substance abuse • Refractory pain	
SETTING:	All	
PERSPECTIVE:	Population	

	CRITERIA	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	**Research Evidence** None **Additional considerations** Patients undergoing the cessation of opioids may experience withdrawal symptoms if they have developed physical dependence on opioids. How to cease opioids quickly and appropriately while avoiding withdrawal symptoms is an area of interest.

BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Yes ☐ No ☐ Uncertain ☒ Yes	• **No randomized controlled trials** compared opioid dosing regimens with the goal of opioid cessation. **BENEFITS and HARMS** • **No trial** reported on **effective cessation of opioid**. • **No trial** reported on **pain relief speed**. • **No trial** reported on **pain relief maintenance**. • **No trial** reported on **QoL**. • **No trial** reported on **functional outcomes**. • **No trial** reported on **confusion**. • **No trial** reported on **gastrointestinal adverse event**. **STRATIFICATIONS** • Studies conducted in adults with a wide age range, without stratification into adolescent, non-older persons, and older persons. • Studies provide no data regarding history of substance abuse. • Studies provide no data regarading refractory pain. **SUMMARY** No eligible trials were found that address this sub-question.

ACCEPTABILITY & PREFERENCES	**Is there important uncertainty or variability about how much people value the options?** Major variability [ ] Minor variability [ ] Uncertain [Yes] **Is the option acceptable to key stakeholders?** Yes [ ] No [ ] Uncertain [Yes]	**<u>Research Evidence</u>** None **<u>Additional considerations</u>** None

FEASIBILITY ./ RESOURCE USE	**How large are the resource requirements?** Major ☐ Minor ☐ Uncertai Yes **Is the option feasible to implement?** Yes ☐ No ☐ Uncertain Yes	**Research Evidence** None **Additional considerations** None
	Would the option improve equity in health? Yes ☐ No ☐ Uncertai Yes	**Research Evidence** None **Additional considerations** None

Recommendation	**Current recommendation:** If the cause of pain is addressed by anticancer treatment, the use of opioids can be stopped. To avoid withdrawal symptoms, the dose should be decreased gradually. After an abrupt reduction in pain (e.g. after nerve block or neuroablative procedure), the dose should be reduced to 25% of the original dose. If the procedure has been successful, the dose can be reduced further every 2-3 days and stopped completely if the pain does not recur. **New (draft) recommendation:** None
Strength of Recommendation	**None**
Quality of Evidence	**None**
Justification	There was no eligible evidence on which to base a recommendation.
Subgroup considerations	
Implementation considerations [incl. M&E]	
Research priorities	

Key Question 5: Adjuvant Treatments

5.1. In adults (including older persons) and adolescents with cancer-related pain are adjuvant steroids more effective than placebo, no steroids, or other steroids to achieve pain control?

The systematic review team have divided Key Question 5.1 into two sections: steroids versus placebo (or no steroid) and comparison of steroids.

5.1.1. Steroids vs. Placebo

Seven eligible studies compared steroids to placebo (see Evidence Profile 5.1) in patients with a variety of cancers. [69-75]; although most studies did not report the cancer types. The studies evaluated methylprednisolone (4 studies), dexamethasone (2 studies), and prednisolone (1 study). Studies were mostly conducted in a wide adults with a wide age range; one was conducted in older adults.[75]

The RCT findings are summarized in Evidence Profile 5.1.1. Five trials provided moderate strength of evidence that pain relief was greater in patients taking steroids than placebo (Forest Plot 5.1.1 below). The summary net difference in pain scores between arms was -9.9 (on a 0 to 100 [worst] scale), 95% CI -16.0 to -3.8, favoring steroids. Over half the weight for this summary estimate came from the only study that found a statistically significant finding, which also reported the greatest reduction in pain scores with steroids, and was published in 1985 (see Evidence Forest Plot 5.1.1 below).
None of the studies reported pain relief speed or duration of pain relief maintenance.

Three studies provided very low strength of evidence that patients taking steroids had improved quality of life compared with placebo (Forest Plot 5.1.2 below), with a summary net difference (on a 0 to 100 [best] scale) of 12.6 (95% CI 6.2, 19.0).Two studies provided very low strength of evidence regarding functional outcomes, using FACT and FACIT, suggesting no difference in functional score (net difference -0.2; 95% CI -2.0, 1.6) or social function (net difference -0.2; 95% CI -2.4, 1.9), both on 0 to 100 scales. The two studies had conflicting findings regarding physical function, with one study finding significant benefit with steroids on the FACIT scale, but the other presenting data that suggested statistically significant worse physical function with steroids on the FACT scale (however, the study implied that they found no significant difference).

One small trial provided very low strength of evidence regarding gastrointestinal bleeds, being the only study to explicitly report this adverse event. No gastrointestinal bleeds occurred among 31 patients in this crossover study. Two small studies reported on psychiatric adverse events. One provided very low strength of evidence regarding depression, failing to provide a precise estimate (RR = 1.00; 95% CI 0.06, 15.2). One provided very low strength of evidence regarding both anxiety and “psychic change” (undefined), also failing to provide precise estimates (both RR = 0.59; 95% CI 0.11, 3.20). No study reported on delirium or psychosis.

Evidence Profile 5.1. Steroids vs. Placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Steroids**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Pain relief (categorical)												
0									not estimable			CRITICAL
Pain relief (continuous) (follow up: range 7 days to 14 days; assessed with VAS, NRS, ESAS-Pain 0-100 [worst] [A])												
5 [1,2,3,4,5]	RCT	serious [B]	not serious	not serious	not serious	none	158	147	**Net Diff −9.9** (−16.0, −3.8) [C]		Moderate	CRITICAL
Pain relief speed												
0									not estimable			IMPORTANT
Pain reduction maintenance												
0									not estimable			CRITICAL
Quality of life (follow up: range 14 days to 8 weeks; assessed with FACIT-F, LASA 0-100 [best] [A])												
3 [1,6,7]	RCT	serious [B]	not serious	serious [D]	not serious	serious [E]	198	209	**Net Diff 12.6** (6.2, 19.0) [F]		Very Low	IMPORTANT
Functional outcomes: Function (follow up: range 8 days to 14 days ; assessed with: FACIT-function, FACT-function; Scale: 0 to 100 [best] [A])												
2 [1,5]	RCT	serious [B]	not serious	serious [D]	serious [G]	none	68	67	**Net Diff -0.2** (-2.0, 1.6)		Very Low	IMPORTANT
Functional outcomes: Physical function (follow up: range 8 days to 14 days ; assessed with: FACIT-physical, FACT-physical; Scale: 0 to 100 [best] [A])												
2 [1,5]	RCT	serious [B]	not serious	serious [D]	very serious [H]	none	68	67	**Conflicting** [I]		Very Low	IMPORTANT
Functional outcomes: Social function (follow up: range 8 days to 14 days ; assessed with: FACIT-social, FACT-social; Scale: 0 to 100 [best] [A])												
2 [1,5]	RCT	serious [B]	not serious	serious [D]	serious [G]	none	68	67	**Net Diff -0.2** (-2.4, 1.9)		Very Low	IMPORTANT
Adverse events: Gastrointestinal bleed (follow up: range 7 days to 8 weeks)												
1 [4]	RCT	not serious	N/A	not serious	very serious [J]	no events	0/31 (0%)	0/31 (0%)	not estimable		Very Low	IMPORTANT
Adverse events: Psychiatric effects (depression, 14 days)												
1 [1]	RCT	not serious	N/A	not serious	very serious [K]	single study	1/67 (1/5%)	1/65 (1.5%)	**RR 1.00** (0.06, 15.2)	**0 difference per 1000** (from 42 fewer to 41 more)	Very Low	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Steroids	Placebo	Relative (95% CI)	Absolute (95% CI)		
Adverse events: Psychiatric effects (anxiety, 7 days)												
1 [3]	RCT	not serious	N/A	not serious	very serious [K]	single study	2/25 (8%)	3/22 (14%)	**RR 0.59** (0.11, 3.20)	**56 fewer per 1000** (from 122 more to 235 fewer)	Very Low	IMPORTANT
Adverse events: Psychiatric effects ("psychic change", 7 days)												
1 [3]	RCT	not serious	N/A	not serious	very serious [K]	single study	2/25 (8%)	3/22 (14%)	**RR 0.59** (0.11, 3.20)	**56 fewer per 1000** (from 122 more to 235 fewer)	Very Low	IMPORTANT
Adverse events: Psychiatric effects (delirium, psychosis)												
0									not estimable			IMPORTANT

Abbreviations: AE: *adverse events****; CI:*** *confidence interval****; ESAS-Pain****: Edmonton Symptom Assessment Scale-Pain;* ***FACIT [-F]:*** *Functional Assessment of Chronic Illness Therapy* ***[****Fatigue****]; FACT****: Functional Assessment of Cancer Therapy****; LASA****: Linear Analog Scale Assessment****; Net Diff****: net difference (between groups)****; NS:*** *not statistically significant****; RCT:*** *randomized controlled trial(s);* ***VAS****: Visual Analog Scale.*

Explanations

A. Scales transformed to 0 to 100, as necessary.
B. Primarily due to high attrition rates.
C. Favoring steroids.
D. FACT and FACIT (total score) are measures of quality of life that mix concepts of both quality of life and functional outcomes. The systematic review team treated the total scores as quality of life measures and the relevant subscores as functional outcomes, but these do not cleanly measure function.
E. Variance data estimated from vague P values (<0.05, <0.01) in two studies. For one study (Popiela 1989 PMID 2483687) unclear what the overall scale was for data provided since they summed a series of subscores; our best understanding was 0-900, but may have been a narrower range.
F. Favoring steroids.
G. Small studies.
H. Small studies providing conflicting findings. No conclusion possible.
I. Yennurajalingam 2013 (PMID 23897970) significantly favored steroids (FACIT Physical). Bruera 2004 (PMID 15471656) significantly favored placebo based on data reported, but implied NS (FACT Physical Well-being).
J. Small trials. No relative estimate possible.
K. Small trials yielding estimate with wide confidence interval.

Trials

1. Yennurajalingam, S., Frisbee-Hume, S., Palmer, J. L., et al. Reduction of cancer-related fatigue with dexamethasone: a double-blind, randomized, placebo-controlled trial in patients with advanced cancer. J Clin Oncol; Sep 01 2013.
2. Twycross, R. G., Guppy, D. Prednisolone in terminal breast and bronchogenic cancer. Practitioner; Jan 1985.
3. Paulsen, O., Klepstad, P., Rosland, J. H., et al. Efficacy of methylprednisolone on pain, fatigue, and appetite loss in patients with advanced cancer using opioids: a randomized, placebo-controlled, double-blind trial. J Clin Oncol; Oct 10 2014.
4. Bruera, E., Roca, E., Cedaro, L., Carraro, S., Chacon, R. Action of oral methylprednisolone in terminal cancer patients: a prospective randomized double-blind study. Cancer Treat Rep; Jul-Aug 1985.
5. Bruera, E., Moyano, J. R., Sala, R., et al. Dexamethasone in addition to metoclopramide for chronic nausea in patients with advanced cancer: a randomized controlled trial. J Pain Symptom Manage; Oct 2004.
6. Popiela, T., Lucchi, R., Giongo, F. Methylprednisolone as palliative therapy for female terminal cancer patients. The Methylprednisolone Female Preterminal Cancer Study Group. Eur J Cancer Clin Oncol; Dec 1989.
7. Della Cuna, G. R., Pellegrini, A., Piazzi, M. Effect of methylprednisolone sodium succinate on quality of life in preterminal cancer patients: a placebo-controlled, multicenter study. The Methylprednisolone Preterminal Cancer Study Group. Eur J Cancer Clin Oncol; Dec 1989.

<table>
<tr><th colspan="3">Evidence-to-Decision table 5.1.1</th></tr>
<tr><td colspan="3">In adults (including older persons) and adolescents with cancer-related pain are adjuvant steroids more effective than no steroids or placebo to achieve pain control?</td></tr>
<tr><td>POPULATION:</td><td>Adults (including older persons) and adolescents with cancer-related pain</td><td rowspan="8">Background:

Steroids are among the most commonly used medications in palliative care, and are commonly used to relieve cancer pain[76]. There use as adjuvant medications has been indicated for management of metastatic bone pain, neuropathic pain, and visceral pain[77].

Current WHO recommendation:

• Corticosteroids are indicated in the following general cases:
○ To improve appetite
○ To enhance sense of well-being
○ To improve strength
○ Hormone therapy
▪ Replacement
▪ Anticancer
○ To relieve pain caused by
▪ Raised intracranial pressure
▪ Nerve compression
▪ Spinal cord compression
▪ Metastatic arthralgia
▪ Bone metastasis
• Corticosteroids are indicated in the following specific cases:
○ Spinal cord compression
○ Nerve compression
○ Dyspnoea:
▪ Pneumonitis (after radiotherapy)
▪ Carcinomatous lymphangitis
▪ Tracheal compression/stridor
○ Superior vena caval obstruction
○ Pericardial effusion</td></tr>
<tr><td>INTERVENTION:</td><td>Steroids (adjuvant)</td></tr>
<tr><td>COMPARISON:</td><td>Placebo (no treatment)</td></tr>
<tr><td>MAIN OUTCOMES:</td><td>• Pain relief
• Pain relief speed
• Pain relief maintenance
• Quality of life (QoL)
• Functional outcomes
• Gastrointestinal bleed (adverse event)
• Psychiatric effects (adverse event)</td></tr>
<tr><td>STRATIFICATIONS:</td><td>• Age (adults, older persons, adolescents, children)
• History of substance abuse
• Refractory pain</td></tr>
<tr><td>SETTING:</td><td>All</td></tr>
<tr><td>PERSPECTIVE:</td><td>Population</td></tr>
</table>

		○ Haemoptysis ○ Obstruction of hollow viscus ▪ Bronchus ▪ Ureter ▪ Intestine ○ Hypercalcaemia (in lymphoma, myeloma) ○ Radiation-induced inflammation ○ Leukoerythroblastic anaemia ○ Rectal discharge (give per rectum) ○ Sweating • Either prednisolone or dexamethasone are recommended, the dose depending on clinical situation. 7mg of prednisolone is equivalent to 1mg of dexamethasone. • For nerve compression pain, prescribe 20-40mg prednisolone/4-6mg of dexamethasone per day. Reduce dose step by step to a maintenance dose after one week. The maintenance dose will depend on the amount necessary to relieve pain, but could be as low as 15mg prednisolone or 2mg dexamethasone. Occasionally, a higher dose may be necessary to achieve significant benefit. • In patients with raised intracranial pressure, an initial daily dose of 8-16mg dexamethasone is appropriate. It may be possible to begin to reduce this to a maintenance dose after one week. With spinal cord compression, even higher doses have been used in some centres – up to 100mg per day initially, reducing to 16mg during radiation therapy. • Adverse events include oedema, dyspeptic symptoms, and occasionally gastrointestinal bleeding. Proximal myopathy, agitation, hypomania, and opportunistic infections may also occur. The incidence of adverse gastrointestinal effects is increased if corticosteroids are used in conjunction with NSAIDs.

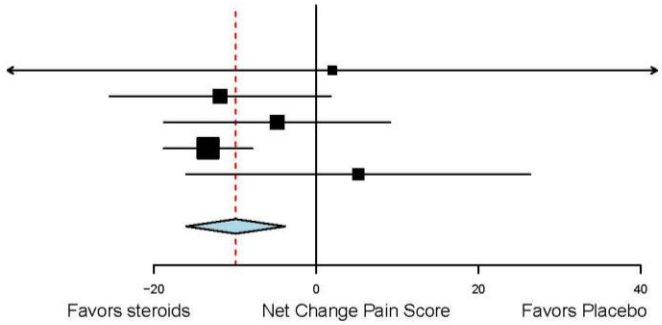
	CRITERIA	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	**Research Evidence** Steroids are among the most commonly used medications in palliative care, and are commonly used to relieve cancer pain[76]. **Additional considerations** The 1996 WHO cancer pain guidelines made recommendations on their use – so too should updated guidelines, which can make use of any evidence developed since the formulation of the previous guidelines.

BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Yes No Uncertain Yes	• **Seven randomized controlled trials** compared steroids to placebo in patients with a variety of cancers; although most studies did not report the cancer types. The studies evaluated methylprednisolone (4 trials), dexamethasone (2 trials), and prednisolone (1 trial). Trials were mostly conducted in adults with a wide age range; one was conducted in older adults. The GDG was of the view that none of the trials were of high enough power to accurately capture rates of adverse events from the therapy. **BENEFITS and HARMS** • **Five trials** provided **moderate strength of evidence** that **pain relief was greater in patients taking steroids than placebo**. The summary net difference in pain scores between arms was -9.9 (on a 0 to 100 [worst] scale), 95% CI -16.0 to -3.8, favoring steroids. • **No trial** reported on **pain relief speed**. • **No trial** reported on **pain relief maintenance**. • **Three trials** provided **low strength of evidence** that **patients taking steroids had improved QoL compared to placebo**, with a summary net difference (on a 0 to 100 [best] scale) of 12.6 (95% CI 6.2, 19.0). • **Two trials** provided **low strength of evidence** regarding functional outcomes, using FACT and FACIT, suggesting **no difference in functional score** (net difference -0.2; 95% CI -2.0, 1.6) or **social function** (net difference -0.2; 95% CI -2.4, 1.9), both on 0 to 100 scales. The two studies had **conflicting findings regarding physical function**, with one study finding significant benefit with steroids on the FACIT scale, but the other presenting data that suggested statistically significant worse physical function with steroids on the FACT scale (however, the study implied that they found no significant difference). • **One trial** provided **very low strength of evidence** regarding gastrointestinal bleeds, being the only study to explicitly report this adverse event. **No gastrointestinal bleeds occurred** among 31 patients in this crossover study. • **Two trials** reported on psychiatric adverse events. **One provided very low strength of evidence regarding depression**, failing to provide a precise estimate (RR = 1.00; 95% CI 0.06, 15.2). **One provided very low strength of evidence regarding both anxiety and "psychic change"** (undefined), also failing to provide precise estimates (both RR = 0.59; 95% CI 0.11, 3.20). No study reported on delirium or psychosis. **STRATIFICATIONS** • Studies conducted in adults with a wide age range, without stratification into adolescent, non-older persons, and older persons. • Studies provide no data regarding history of substance abuse. • Studies provide no data regarading refractory pain. **SUMMARY**

Steroids probably improve pain relief and may improve QoL. We are uncertain whether in this population steroids increase risks of gastrointestinal bleeds or psychiatric adverse events.

Forest Plot 5.1.1. Pain Relief (Continuous Scale) Steroids vs. Placebo

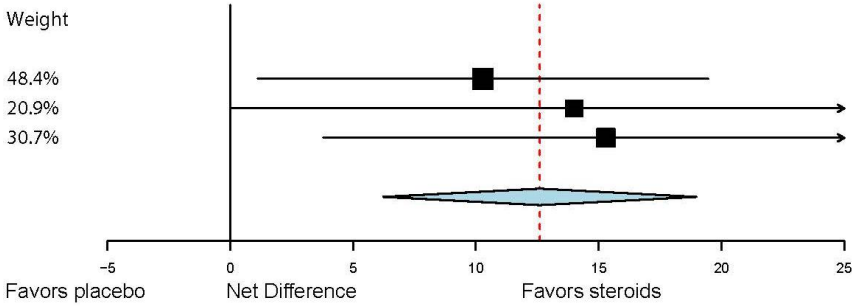
Studies	Estimate (95% C.I.)	Weight
Bruera 2004	2.00 (−38.00, 42.00)	2.28%
Yennurajalingam 2013	−11.80 (−25.44, 1.84)	16.8%
Paulsen 2014	−4.80 (−18.75, 9.15)	16.2%
Bruera 1985	−13.30 (−18.77, −7.83)	57.0%
Twycross 1985	5.20 (−16.00, 26.40)	7.69%
Overall (I^2=16.13%, P=0.39)	−9.90 (−16.01, −3.79)	



***Abbreviation**: **CI**: confidence interval.*

BENEFITS & HARMS (CONT.)

Forest Plot 5.1.1. Quality of Life (Continuous Scale) Steroids vs. Placebo



Scores from individual studies have been transformed to a uniform 0-100 scale (100 = best).

ACCEPTABILITY & PREFERENCES	**Is there important uncertainty or variability about how much people value the options?** Major variability Yes Minor variability Uncertain **Is the option acceptable to key stakeholders?** Yes No Uncertain Yes	**Research evidence** None presented. **Additional considerations** The GDG remarked that patients, especially young patients, are sometimes reluctant to take the medications due to their common side effects. Older patients are also sometimes reluctant on account of diabetes and other comorbidities. The GDG deemed the option acceptable to clinicians, who frequently appreciate the speed of onset of steroids' beneficial effects.

FEASIBILITY ./ RESOURCE USE

How large are the resource requirements?

Major	Minor	Uncertai
Yes		

Is the option feasible to implement?

Yes	No	Uncertain
Yes		

	Price per 1mg	Defined daily dose
Dexamethasone (Source:[78])	USD $ 0.02475	1.5mg
Prednisolone (Source:[79])	USD $ 0.00222	10mg
Methylprednisolone (Source:[80])	USD $ 0.0104	20mg

Additional considerations

The resource requirements are evidently small.

The GDG deemed the option feasible.

Would the option improve equity in health?

Yes	No	Uncertai
		Yes

Research Evidence

None

Additional considerations

The GDG did not believe the therapy would have much impact on equity.

Recommendation	**Current recommendation:**
	Corticosteroids are indicated in the following general cases:
	
	• To improve appetite
	• To enhance sense of well-being
	• To improve strength
	• Hormone therapy
	  o Replacement
	  o Anticancer
	• To relieve pain caused by
	  o Raised intracranial pressure
	  o Nerve compression
	  o Spinal cord compression
	  o Metastatic arthralgia
	  o Bone metastasis
	Corticosteroids are indicated in the following specific cases:
	
	• Spinal cord compression
	• Nerve compression
	• Dyspnoea:
	  o Pneumonitis (after radiotherapy)
	  o Carcinomatous lymphangitis
	  o Tracheal compression/stridor
	• Superior vena caval obstruction
	• Pericardial effusion
	• Haemoptysis
	• Obstruction of hollow viscus
	  o Bronchus
	  o Ureter
	  o Intestine
	• Hypercalcaemia (in lymphoma, myeloma)
	• Radiation-induced inflammation
	• Leukoerythroblastic anaemia

	• Rectal discharge (give per rectum) • Sweating Either prednisolone or dexamethasone are recommended, the dose depending on clinical situation. 7mg of prednisolone is equivalent to 1mg of dexamethasone. For nerve compression pain, prescribe 20-40mg prednisolone/4-6mg of dexamethasone per day. Reduce dose step by step to a maintenance dose after one week. The maintenance dose will depend on the amount necessary to relieve pain, but could be as low as 15mg prednisolone or 2mg dexamethasone. Occasionally, a higher dose may be necessary to achieve significant benefit. In patients with raised intracranial pressure, an initial daily dose of 8-16mg dexamethasone is appropriate. It may be possible to begin to reduce this to a maintenance dose after one week. With spinal cord compression, even higher doses have been used in some centres – up to 100mg per day initially, reducing to 16mg during radiation therapy. Adverse events include oedema, dyspeptic symptoms, and occasionally gastrointestinal bleeding. Proximal myopathy, agitation, hypomania, and opportunistic infections may also occur. The incidence of adverse gastrointestinal effects is increased if corticosteroids are used in conjunction with NSAIDs. **New (draft) recommendation:** In adults (including older persons) and adolescents, with pain related to active cancer, adjuvant steroids should be given to achieve pain control, based on clinical indications.
Strength of Recommendation	**Strong**
Quality of Evidence	➢ **MODERATE** [Pain (critical) = moderate QoL (important) = low others omitted for no data, conflicting, no difference, or indeterminate findings]

Justification	The GDG noted that while some side effect and adverse events from steroids can be serious, the balance of effects is evidently strongly in favour of their use when indicated. Care should be taken with regard to patient selection for the prescription of steroids to avoid contraindications. The GDG also agreed that in the text of the guidelines, in line with good clinical practice, the steroids should only be prescribed for as short a period as possible.
Subgroup considerations	
Implementation considerations [incl. M&E]	
Research priorities	

5.1.2. Comparison of Steroids

No eligible studies were found that address this sub-question.

<table>
<tr><th colspan="3">Evidence-to-Decision table 5.1.2</th></tr>
<tr><td colspan="3">In adults (including older persons) and adolescents with cancer-related pain are adjuvant steroids more effective than other steroids or placebo to achieve pain control?</td></tr>
<tr><td>POPULATION:</td><td>Adults (including older persons) and adolescents with cancer-related pain</td><td rowspan="7">Background:

Steroids are among the most commonly used medications in palliative care, and are commonly used to relieve cancer pain[76]. They are particularly useful as adjuvant medications for management of metastatic bone pain, neuropathic pain, and visceral pain[77].

Current WHO recommendation:

• Corticosteroids are indicated in the following general cases:
○ To improve appetite
○ To enhance sense of well-being
○ To improve strength
○ Hormone therapy
▪ Replacement
▪ Anticancer
○ To relieve pain caused by
▪ Raised intracranial pressure
▪ Nerve compression
▪ Spinal cord compression
▪ Metastatic arthralgia
▪ Bone metastasis
• Corticosteroids are indicated in the following specific cases:
○ Spinal cord compression
○ Nerve compression
○ Dyspnoea:
▪ Pneumonitis (after radiotherapy)
▪ Carcinomatous lymphangitis</td></tr>
<tr><td>INTERVENTION:</td><td>Steroids</td></tr>
<tr><td>COMPARISON:</td><td>Steroids</td></tr>
<tr><td>MAIN OUTCOMES:</td><td>• Pain relief
• Pain relief speed
• Pain relief maintenance
• Quality of life (QoL)
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<tr><td>STRATIFICATIONS:</td><td>• Age (adults, older persons, adolescents, children)
• History of substance abuse
• Refractory pain</td></tr>
<tr><td>SETTING:</td><td>All</td></tr>
<tr><td>PERSPECTIVE:</td><td>Population</td></tr>
</table>

		▪ Tracheal compression/stridor ○ Superior vena caval obstruction ○ Pericardial effusion ○ Haemoptysis ○ Obstruction of hollow viscus ▪ Bronchus ▪ Ureter ▪ Intestine ○ Hypercalcaemia (in lymphoma, myeloma) ○ Radiation-induced inflammation ○ Leukoerythroblastic anaemia ○ Rectal discharge (give per rectum) ○ Sweating • Either prednisolone or dexamethasone are recommended, the dose depending on clinical situation. 7mg of prednisolone is equivalent to 1mg of dexamethasone. • For nerve compression pain, prescribe 20-40mg prednisolone/4-6mg of dexamethasone per day. Reduce dose step by step to a maintenance dose after one week. The maintenance dose will depend on the amount necessary to relieve pain, but could be as low as 15mg prednisolone or 2mg dexamethasone. Occasionally, a higher dose may be necessary to achieve significant benefit. • In patients with raised intracranial pressure, an initial daily dose of 8-16mg dexamethasone is appropriate. It may be possible to begin to reduce this to a maintenance dose after one week. With spinal cord compression, even higher doses have been used in some centres – up to 100mg per day initially, reducing to 16mg during radiation therapy. • Adverse events include oedema, dyspeptic symptoms, and occasionally gastrointestinal bleeding. Proximal myopathy, agitation, hypomania, and opportunistic infections may also occur. The incidence of adverse gastrointestinal effects is increased if corticosteroids are used in conjunction with NSAIDs.

	CRITERIA	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	**Research Evidence** Steroids are among the most commonly used medications in palliative care, and are commonly used to relieve cancer pain[76]. **Additional considerations** The 1996 WHO cancer pain guidelines made recommendations on their use – so too should updated ones, which can make use of evidence developed since the formulation of the previous guidelines.

BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Yes ☐ No ☐ Uncertain ☒ Yes	• **No randomized controlled trials** compared steroids to other steroids. **BENEFITS and HARMS** • **No trial** reported on **pain relief**. • **No trial** reported on **pain relief speed**. • **No trial** reported on **pain relief maintenance**. • **No trial** reported on **QoL**. • **No trial** reported on **functional outcomes**. • **No trial** reported on **gastrointestinal bleed**. • **No trial** reported on **psychiatric effects**. **STRATIFICATIONS** • Studies conducted in adults with a wide age range, without stratification into adolescent, non-older persons, and older persons. • Studies provide no data regarding history of substance abuse. • Studies provide no data regarading refractory pain. **SUMMARY** No eligible trials were found that address this sub-question.

ACCEPTABILITY & PREFERENCES	**Is there important uncertainty or variability about how much people value the options?** Major variability [ ] Minor variability [ ] Uncertain [Yes] **Is the option acceptable to key stakeholders?** Yes [ ] No [ ] Uncertain [Yes]	**<u>Research Evidence</u>** None **<u>Additional considerations</u>** None

FEASIBILITY ./ RESOURCE USE

How large are the resource requirements?

Major	Minor	Uncertai
	Yes	

Is the option feasible to implement?

Yes	No	Uncertain
		Yes

	Price per 1mg	Defined daily dose
Dexamethasone (Source:[78])	USD $ 0.02475	1.5mg
Prednisolone (Source:[79])	USD $ 0.00222	10mg
Methylprednisolone (Source:[80])	USD $ 0.0104	20mg

Would the option improve equity in health?

Yes	No	Uncertai
		Yes

Research Evidence

None

Additional considerations

None

Recommendation	**Current recommendation:**
	• Corticosteroids are indicated in the following general cases:
	  ○ To improve appetite
	  ○ To enhance sense of well-being
	  ○ To improve strength
	  ○ Hormone therapy
	  ▪ Replacement
	  ▪ Anticancer
	  ○ To relieve pain caused by
	  ▪ Raised intracranial pressure
	  ▪ Nerve compression
	  ▪ Spinal cord compression
	  ▪ Metastatic arthralgia
	  ▪ Bone metastasis
	• Corticosteroids are indicated in the following specific cases:
	  ○ Spinal cord compression
	  ○ Nerve compression
	  ○ Dyspnoea:
	  ▪ Pneumonitis (after radiotherapy)
	  ▪ Carcinomatous lymphangitis
	  ▪ Tracheal compression/stridor
	  ○ Superior vena caval obstruction
	  ○ Pericardial effusion
	  ○ Haemoptysis
	  ○ Obstruction of hollow viscus
	  ▪ Bronchus
	  ▪ Ureter
	  ▪ Intestine
	  ○ Hypercalcaemia (in lymphoma, myeloma)
	  ○ Radiation-induced inflammation
	  ○ Leukoerythroblastic anaemia
	  ○ Rectal discharge (give per rectum)
	  ○ Sweating

	• Either prednisolone or dexamethasone are recommended, the dose depending on clinical situation. 7mg of prednisolone is equivalent to 1mg of dexamethasone. • For nerve compression pain, prescribe 20-40mg prednisolone/4-6mg of dexamethasone per day. Reduce dose step by step to a maintenance dose after one week. The maintenance dose will depend on the amount necessary to relieve pain, but could be as low as 15mg prednisolone or 2mg dexamethasone. Occasionally, a higher dose may be necessary to achieve significant benefit. • In patients with raised intracranial pressure, an initial daily dose of 8-16mg dexamethasone is appropriate. It may be possible to begin to reduce this to a maintenance dose after one week. With spinal cord compression, even higher doses have been used in some centres – up to 100mg per day initially, reducing to 16mg during radiation therapy. • Adverse events include oedema, dyspeptic symptoms, and occasionally gastrointestinal bleeding. Proximal myopathy, agitation, hypomania, and opportunistic infections may also occur. The incidence of adverse gastrointestinal effects is increased if corticosteroids are used in conjunction with NSAIDs. **New (draft) recommendation:** **None**
Strength of Recommendation	
Quality of Evidence	
Justification	There were no trials that compared the effects of different steroids, only trials that compared the steroids with placebo. Therefore, the GDG could not make a recommendation for one steroid over others.
Subgroup considerations	
Implementation considerations [incl. M&E]	
Research priorities	

5.2. In adults (including older persons) and adolescents with bone metastases, what is the evidence for the use of bisphosphonates or monoclonals compared with each other or no treatment or other bisphosphonates in order to prevent and treat pain

The systematic review team have divided Key Question 5.2 into five sections: bisphosphonates versus placebo, comparisons of bisphosphonates, monoclonal antibodies (hereafter monoclonals) versus placebo, comparisons of monoclonals, and bisphosphonates versus monoclonals.

5.2.1. Bisphosphonates vs. Placebo

Forty eligible studies compared bisphosphonates to placebo (see Evidence Profile 5.2.1).[81-120] Most study participants had either breast or prostate cancer. Fifteen of the studies were restricted to people (women or men) with breast cancer (or included mostly people with breast cancer). Ten studies were restricted to men with prostate cancer. Two additional studies included mostly people with breast or prostate cancer. The third most common cancer across studies was lung cancer. Thirteen studies evaluated clodronate, nine zole~~n~~dronate, five each ibandronate and pamidronate, and one each etidronate and risendronate.

There is moderate strength of evidence of greater pain relief with use of bisphosphonates compared with placebo among patients with painful bone metastases. Seven trials evaluated categorical pain relief; however, four evaluated improvements in pain (e.g., reductions of at least 2 points on a 5 point pain scale) [89,99,109,117] and three evaluated complete pain relief.[86,96,107] The studies were mostly vague about whether they were assessing overall cancer pain or metastatic bone pain. Four studies evaluated clodronate and one each etidronate, pamidronate, and risedronate. Although favoring use of bisphosphonates, no statistically significant difference in complete relief of pain (RR 1.61; 95% CI 0.89, 2.93) or pain improvement (RR 1.24; 95% CI 0.90, 1.71) were found (see Forest Plots 5.2.1.1 and 5.2.1.2 below). Fourteen trials evaluated pain on continuous scales (which were each converted to a 100 point scale, with 100 = worst pain). [83,85,87-89,97,98,101,104,105,108,111,113,119] Six studies evaluated clodronate, three pamidronate, and one each ibandronate and zoledronate. The studies, overall, indicated statistically significant improvement in pain, with an overall net difference of -11.8 (95% CI -17.6, -6.1) (See Forest Plot 5.2.1.3 below).

No study evaluated speed of pain relief. A single study provided low strength of evidence suggesting no significant difference in duration of pain relief between risendronate and placebo in people with prostate cancer. The study reported HR = 1.27 (95% CI 0.84, 1.92), favoring placebo (3.4 month median duration with risendronate, 5.5 months with placebo).

Twenty-five studies evaluated the various skeletal-related events.[85,90,92-95,97,100,102,103,105,108,110,114,118-128] Fourteen of the studies included people with breast cancer (or mostly breast cancer), four prostate cancer, three lung cancer (or mostly lung cancer), and one bladder cancer. Nine of the studies evaluated ~~zolendronate~~zoledronate, five ibandronate, and four each clodronate and pamidronate. Overall, the studies provided moderate strength of evidence that bisphosphonates reduce the risk of skeletal-related events. The six studies that reported hazard ratios for time to first skeletal-related event (any) in comparisons of ~~zolendronate~~zoledronate (4 studies) or ibandronate (2 studies) found a statistically significant

benefit of bisphosphonates over placebo (HR = 0.71; 95% CI 0.61, 0.84).[82,90,92,106,110,119] Eighteen studies found a reduction in risk of any skeletal-related event yielding a summary RR of 0.81 (95% CI 0.76, 0.86) (see Forest Plot 5.2.1.4 below).[81,82,90-95,97,100,106,108,110-112,118-120]

Twelve trials also found a reduction in risk of fracture with bisphosphonates (RR = 0.75; 95% CI 0.67, 0.84) (see Forest Plot 5.2.1.5 below). Eight trials nominally favored bisphosphonates to reduce the risk of spinal cord compressions (RR = 0.74; 95% CI 0.49, 1.12) (see Forest Plot 5.2.1.6 below). The three ~~zolendronate~~zoledronate studies together found a statistically significant reduction in risk of spinal cord compression (RR = 0.52; 95% CI 0.27, 0.99), but this result was not significantly different than the nonsignificant summary of the pamidronate studies (RR = 1.07; 95% CI 0.60, 1.90; P=0.72 between studies of different medications).

The 12 studies that reported on bone radiotherapy found a significantly reduced risk with bisphosphonates (RR = 0.71; 95% CI 0.63, 0.81) (see Forest Plot 5.2.1.7 below). Nine studies also found a significantly reduced risk of bone surgeries with bisphosphonates (RR = 0.62; 95% CI 0.44, 0.89) (see Forest Plot 5.2.1.8 below). A significantly greater risk reduction was found in the four studies of pamidronate (RR = 0.53; 95% CI 0.39, 0.74) than the two studies of ~~zolendronate~~zoledronate (RR = 1.23; 95% CI 0.60, 2.51; P=0.042 between studies of different medications).

Thirteen studies reported on risk of hypercalcemia with bisphosphonates (see Forest Plot 5.2.1.9 below). Overall, bisphosphonates lowered the risk of hypercalcemia compared with placebo (RR = 0.47; 95% CI 0.37, 0.60). The studies of ~~zolendronate~~zoledronate (RR = 0.30; 95% CI 0.12, 0.74) and pamidronate (RR = 0.41; 95% CI 0.29, 0.57) showed a nominally stronger effect on hypercalcemia than studies of clodronate (RR = 0.65; 95% CI 0.43, 0.96), but the differences among studies of different medications were not statistically significant (P=0.072).

Five studies provide varying strength of evidence that bisphosphonates do not affect quality of life compared with placebo. [84,85,89,92,105]The studies evaluated clodronate (3 studies), ibandronate (1 study), and ~~zolendronate~~zoledronate (1 study). The five studies provided very low strength of evidence of no significant difference in changes in quality of life scores measured on a variety of scales (summary net difference on a 0 to 100 [best] scale = 8; 95% CI -6, 22), but one study provided moderate strength of evidence of reduced and delayed deterioration in quality of life with clodronate (RR = 0.81; 95% CI 0.67, 0.99 and HR = 0.71; 95% CI 0.56, 0.92).[84]

Two studies provided very low to low strength of evidence of small improvements in functional outcomes with bisphosphonates compared with placebo.[92,97] One study each found net differences (all transformed to 100 point scale where 100 = best score) in ECOG performance status of -7.7 (95% CI -17.0, 1.7), in FACT-P physical well-being of 1.4 (95% CI 0.5, 3.3), in FACT-P social well-being of 1.8 (95% CI 1.0, 2.6), and in FACT-P functional well-being of 1.8 (95% CI 0.6, 2.9). However, it should be noted that these confidence intervals are estimated from reported data and for the FACT-P scores, the study implied they found no significant differences between ~~zolendronate~~zoledronate and placebo.

Four studies explicitly reported on the risk of osteonecrosis of the jaw.[83,99,106,116] Across the studies, there were no occurrences of this adverse event with either bisphosphonates (N=460) or placebo (N=450).

Evidence Profile 5.2.1. Bisphosphonates vs. Placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bisphosphonates	Placebo	Relative (95% CI)	Absolute (95% CI)		
Pain Relief (categorical), complete (follow up: range 24 weeks to 6 months)												
3 [1,2,3]	RCT	not serious	not serious	serious [A]	not serious	none	22/84 (27% [B])	14/88 (16% [B])	**RR 1.61** (0.89, 2.93)	**97 more per 1000** (from 18 fewer to 306 more)	Moderate	CRITICAL
Pain Relief (categorical), improvement (follow up: range 4 weeks to 48 months; assessed with PPI 0-100 [worst] [C])												
4 [4,5,6,7]	RCT	not serious	not serious	serious [A]	not serious	none	61/210 (22% [B])	50/232 (16% [B])	**RR 1.24** (0.90, 1.71)	**38 more per 1000** (from 16 fewer to 113 more)	Moderate	CRITICAL
Pain Relief (continuous) (follow up: range 1 week to 96 weeks)												
14 [7,8,9,10,11,12,13,14,15,16,17,18,19,20]	RCT	not serious	not serious	serious [A]	not serious	none	1174	1196	**Net Diff -11.8** (-17.6, -6.12), favoring bisphosphonate		Moderate	CRITICAL
Pain relief speed												
0									not estimable			IMPORTANT
Pain reduction maintenance (follow up: 3 years)												
1 [21]	RCT	serious [D]	N/A	not serious	not serious	single study	283	286	**HR 1.27** (0.84, 1.92) 3.4 vs. 5.5 months		Low	CRITICAL
Skeletal Related Events, any (follow up: range 1 year to 7 years)												
20 [8,9,10,11,14,20,22,23,24,25,26,27,28,29,30,31,32,33,34,40]	RCT	serious [E]	not serious	not serious	not serious	none	**Any SRE (RR)** 1571/3569 (44% [B,F])	1621/2989 (54% [B,G])	**RR 0.81** (0.76, 0.86)	**104 fewer per 1000** (from 76 to 130 fewer)	Moderate	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bisphosphonates	Placebo	Relative (95% CI)	Absolute (95% CI)		
							Any SRE (HR) 1604	1325	**HR 0.71** (0.61, 0.84)			
Skeletal Related Events, fracture (follow up: range 27 weeks to 72 months)												
12 [9,10,11,14,20,24,26,27,34,35,36,37]	RCT	serious [E]	not serious	not serious	not serious	none	386/1972 (20% [B,H])	467/1561 (30% [B,I])	**RR 0.75** (0.67, 0.84)	**58 fewer per 1000** (from 37 to 77 fewer)	Moderate	IMPORTANT
Skeletal Related Events, spinal cord compression (follow up: range 27 weeks to 72 months)												
8 [9,10,11,14,24,27,34,36]	RCT	serious [E]	not serious	not serious	not serious	none	42/1464 (2.9% [B,J])	50/1211 (4.1% [B,K])	**RR 0.74** (0.49, 1.12) [L]	**11 fewer per 1000** (from 4 more to 21 fewer)	Moderate	IMPORTANT
Skeletal Related Events, radiotherapy (follow up: range 6 months to 3 years)												
12 [9,10,14,24,26,27,28,30,34,35,37,38]	RCT	serious [E]	not serious	not serious	not serious	none	471/1944 (24% [B,M])	573/1694 (34% [B,N])	**RR 0.71** (0.63, 0.81)	**76 fewer per 1000** (from 47 to 102 fewer)	Moderate	IMPORTANT
Skeletal Related Events, bone surgery (follow up: range 27 weeks to 2 years)												
9 [9,10,14,27,30,34,35,37,39]	RCT	serious [E]	not serious	not serious	not serious	none	77/1744 (4.4% [B,O])	110/1488 (7.4% [B,P])	**RR 0.62** (0.44, 0.89) [Q]	**22 fewer per 1000** (from 1 to 36 fewer)	Moderate	IMPORTANT
Skeletal Related Events, hypercalcemia (follow up: range 6 months to 3 years)												
13 [9,10,11,14,25,26,27,28,30,34,35,37,38]	RCT	serious [E]	not serious	not serious	not serious	none	81/1497 (5.4% [B,R])	188/1522 (12% [B,S])	**RR 0.47** (0.37, 0.60) [T]	**59 fewer per 1000** (from 43 to 71 fewer)	Moderate	IMPORTANT
Quality of Life (follow up: range 6 months to 2 years; assessed with EORTC QLQ-C30, FACT-P; Scale: 0-100 [best] [B])												
5 [7,11,20,21,29]	RCT	not serious	serious [U]	serious [V]	serious [W]	none	3521	3005	**Net Difference 8** (-6, 22), favoring bisphosphonate		Very Low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bisphosphonates	Placebo	Relative (95% CI)	Absolute (95% CI)		
Quality of Life (follow up: 59 months [months]; worsened WHO performance status by at least one grade)												
1 [21]	RCT	not serious	N/A	not serious	not serious	single study	79/155 (51%)	98/156 (63%)	**RR 0.81** (0.67, 0.99) **HR 0.71** (0.56, 0.92), favoring bisphosphonate		Moderate	CRITICAL
Functional Outcomes (follow-up: 24 months; assessed with ECOG performance status, scale 0 to 100 [best] [B])												
1 [14]	RCT	not serious	N/A	not serious	serious [X]	single study	119	104	**Net Diff -7.7** (-17.0, 1.7), favoring pamidronate		Low	IMPORTANT
Functional Outcomes (follow-up 24 months; assessed with FACT-P Physical Well-Being Score, scale 0 to 100 [best] [B])												
1 [28]	RCT	serious [X]	N/A	serious [V]	serious [Y]	single study	2993	2901	**Diff 1.4** (0.5, 3.3), [Z] favoring pamidronate		Very Low	IMPORTANT
Functional Outcomes (follow-up 24 months; assessed with FACT-P Social Well-Being Score, scale 0 to 100 [best] [B])												
1 [28]	RCT	serious [X]	N/A	serious [V]	serious [Y]	single study	3000	2914	**Diff 1.8** (1.0, 2.6), [Z] favoring pamidronate		Very Low	IMPORTANT
Functional Outcomes (follow-up 24 months; assessed with FACT-P Functional Well-Being Score, scale 0 to 100 [best] [B])												
1 [28]	RCT	serious [X]	N/A	serious [V]	serious [Y]	single study	3000	2914	**Diff 1.8** (0.6, 2.9), [Z] favoring pamidronate		Very Low	IMPORTANT
Adverse Events: Osteonecrosis of jaw (1 to 4 years)												
4 [6,19,24,34]	RCT	not serious	not serious	not serious	serious [AA]	no events	0/460 (0%)	0/450 (0%)	not estimable		Low	IMPORTANT

Abbreviations: CI: *Confidence interval;* ***Diff****: difference (between groups);* ***EORTC QLQ-C30****: European Organization for Research and Treatment of Cancer Quality Of Life Questionnaire Core-30;* ***FACT****: Functional Assessment of Cancer Therapy;* ***GI****: gastrointestinal;* ***HR****: hazard ratio;* ***N/A****: not applicable;* ***NS****: not statistically significant;* ***PPI****: Present Pain Intensity;* ***RCT****: randomized controlled trial(s);* ***RR****: relative risk (log scale);* ***SRE****: skeletal-related events.*

Explanations

A. Unclear whether measured pain was overall cancer pain or metastatic bone pain
B. Meta-analyzed value.
C. Scales transformed to 0 to 100, as necessary.
D. Unblinded

E. Issues with lack of blinding, poor allocation concealment, and poor reporting.
F. Median 45% (Range 4.6-60).
G. Median 54% (Range 5.3, 91).
H. Median 15% (Range 0, 45).
I. Median 21% (Range 3.2, 54).
J. Median 3.0% (Range 0, 3.8).
K. Median 4.0% (Range 1.7, 12).
L. Pamidronate studies were nonsignificant with RR 1.07 (0.60, 1.90) but Zoledronate studies had RR 0.52 (0.27, 0.99) However, the difference in effect between the two sets of studies was nonsignificant (P=0.072).
M. Median 20% (Range 8.8-40).
N. Median 32% (Range 7.8-48).
O. Median 4.3% (Range 0-7.1).
P. Median 6.7% (Range 0.9-12).
Q. The subset of pamidronate studies were statistically significant in contrast to the ~~zolendronate~~zoledronate studies (P=0.041 between bisphosphonates). See Forest Plot 5.2.2 SRE Surgery.
R. Median 4.4% (Range 0-24).
S. Median 10% (Range 1.1-35).
T. The three subsets of studies based on medication used were not significantly different than each other; however, the three ~~zolendronate~~zoledronate studies had a stronger effect than the other two medications, although the difference was not statistically significant (P=0.072). See Forest Plot 5.2.2 SRE Hypercalcemia.
U. Wide range of normalized net differences, from -3.2 to 31 (where 100=best). Significant statistical heterogeneity.
V. EORTC and FACT (total score) are measures of quality of life that mix concepts of both quality of life and functional outcomes. The systematic review treated the total scores as quality of life measures and the relevant subscores as functional outcomes, but these do not cleanly measure function.
W. Highly imprecise. Two studies reported only median values and ranges.
X. Small study.
Y. Issues with lack of blinding and poor reporting.
Z. Difference and confidence interval estimated from reported data, but study implied no significant difference.
AA. Not estimable.

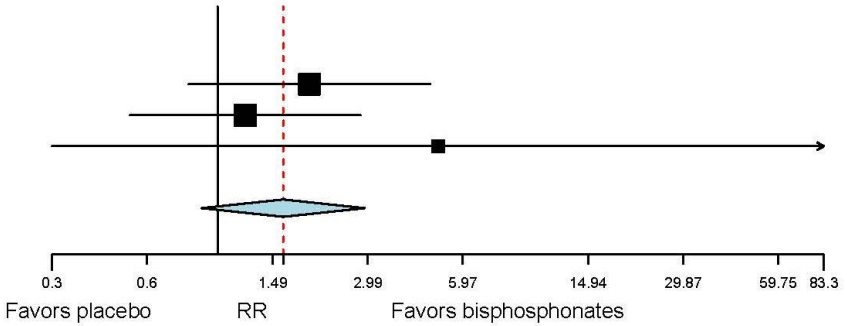
Trials

1. Siris, E. S., Hyman, G. A., Canfield, R. E.. Effects of dichloromethylene diphosphonate in women with breast carcinoma metastatic to the skeleton. Am J Med; Mar 1983.
2. Kylmala, T., Tammela, T., Risteli, L., Risteli, J., Taube, T., Elomaa, I.. Evaluation of the effect of oral clodronate on skeletal metastases with type 1 collagen metabolites. A controlled trial of the Finnish Prostate Cancer Group. Eur J Cancer; 1993.
3. Elomaa, I., Kylmala, T., Tammela, T., Viitanen, J., Ottelin, J., Ruutu, M., Jauhiainen, K., Ala-Opas, M., Roos, L., Seppanen, J., et al., . Effect of oral clodronate on bone pain. A controlled study in patients with metastic prostatic cancer. Int Urol Nephrol; 1992.
4. Vinholes, J. J., Purohit, O. P., Abbey, M. E., Eastell, R., Coleman, R. E.. Relationships between biochemical and symptomatic response in a double-blind randomised trial of pamidronate for metastatic bone disease. Ann Oncol; Dec 1997.
5. Smith, J. A.,Jr.. Palliation of painful bone metastases from prostate cancer using sodium etidronate: results of a randomized, prospective, double-blind, placebo-controlled study. J Urol; Jan 1989.
6. Meulenbeld, H. J., van Werkhoven, E. D., Coenen, J. L., Creemers, G. J., Loosveld, O. J., de Jong, P. C., Ten Tije, A. J., Fossa, S. D., Polee, M., Gerritsen, W., Dalesio, O., de Wit, R.. Randomised phase II/III study of docetaxel with or without risedronate in patients with metastatic Castration Resistant Prostate Cancer (CRPC), the Netherlands Prostate Study (NePro). Eur J Cancer; Nov 2012.
7. Ernst, D. S., Tannock, I. F., Winquist, E. W., Venner, P. M., Reyno, L., Moore, M. J., Chi, K., Ding, K., Elliott, C., Parulekar, W.. Randomized, double-blind, controlled trial of mitoxantrone/prednisone and clodronate versus mitoxantrone/prednisone and placebo in patients with hormone-refractory prostate cancer and pain. J Clin Oncol; Sep 01 2003.
8. Zaghloul, M. S., Boutrus, R., El-Hossieny, H., Kader, Y. A., El-Attar, I., Nazmy, M.. A prospective, randomized, placebo-controlled trial of zoledronic acid in bony metastatic bladder cancer. Int J Clin Oncol; Aug 2010.
9. Theriault, R. L., Lipton, A., Hortobagyi, G. N., Leff, R., Gluck, S., Stewart, J. F., Costello, S., Kennedy, I., Simeone, J., Seaman, J. J., Knight, R. D., Mellars, K., Heffernan, M., Reitsma, D. J.. Pamidronate reduces skeletal morbidity in women with advanced breast cancer and lytic bone lesions: a randomized, placebo-controlled trial. Protocol 18 Aredia Breast Cancer Study Group. J Clin Oncol; Mar 1999.
10. Small, E. J., Smith, M. R., Seaman, J. J., Petrone, S., Kowalski, M. O.. Combined analysis of two multicenter, randomized, placebo-controlled studies of pamidronate disodium for the palliation of bone pain in men with metastatic prostate cancer. J Clin Oncol; Dec 01 2003.
11. Robertson, A. G., Reed, N. S., Ralston, S. H.. Effect of oral clodronate on metastatic bone pain: a double-blind, placebo-controlled study. J Clin Oncol; Sep 1995.
12. Piga, A., Bracci, R., Ferretti, B., Sandri, P., Nortilli, R., Acito, L., Pancotti, A., Di Furia, L., Carle, F., Cellerino, R.. A double blind randomized study of oral clodronate in the treatment of bone metastases from tumors poorly responsive to chemotherapy. J Exp Clin Cancer Res; Jun 1998.
13. O'Rourke, N., McCloskey, E., Houghton, F., Huss, H., Kanis, J. A.. Double-blind, placebo-controlled, dose-response trial of oral clodronate in patients with bone metastases. J Clin Oncol; Apr 1995.
14. Lipton, A., Theriault, R. L., Hortobagyi, G. N., Simeone, J., Knight, R. D., Mellars, K., Reitsma, D. J., Heffernan, M., Seaman, J. J.. Pamidronate prevents skeletal complications and is effective palliative treatment in women with breast carcinoma and osteolytic bone metastases: long term follow-up of two randomized, placebo-controlled trials. Cancer; Mar 01 2000.
15. Ernst, D. S., MacDonald, R. N., Paterson, A. H., Jensen, J., Brasher, P., Bruera, E.. A double-blind, crossover trial of intravenous clodronate in metastatic bone pain. J Pain Symptom Manage; Jan 1992.
16. Ernst, D. S., Brasher, P., Hagen, N., Paterson, A. H., MacDonald, R. N., Bruera, E.. A randomized, controlled trial of intravenous clodronate in patients with metastatic bone disease and pain. J Pain Symptom Manage; Jun 1997.
17. Tubiana-Hulin, M., Beuzeboc, P., Mauriac, L., Barbet, N., Frenay, M., Monnier, A., Pion, J. M., Switsers, O., Misset, J. L., Assadourian, S., Bessa, E.. [Double-blinded controlled study comparing clodronate versus placebo in patients with breast cancer bone metastases]. Bull Cancer; Jul 2001.
18. Martoni, A., Guaraldi, M., Camera, P., Biagi, R., Marri, S., Beghe, F., Pannuti, F.. Controlled clinical study on the use of dichloromethylene diphosphonate in patients with breast carcinoma metastasizing to the skeleton. Oncology; 1991.
19. Broom, R. J., Hinder, V., Sharples, K., Proctor, J., Duffey, S., Pollard, S., Fong, P. C., Forgeson, G., Harris, D. L., Jameson, M. B., O'Donnell, A., North, R. T., Deva, S., Hanning, F. J., Grey, A., Findlay, M. P.. Everolimus and zoledronic acid in patients with renal cell carcinoma with bone metastases: a randomized first-line phase II trial. Clin Genitourin Cancer; Feb 2015.

20. Diel, I. J., Body, J. J., Lichinitser, M. R., Kreuser, E. D., Dornoff, W., Gorbunova, V. A., Budde, M., Bergstrom, B.. Improved quality of life after long-term treatment with the bisphosphonate ibandronate in patients with metastatic bone disease due to breast cancer. Eur J Cancer; Jul 2004.
21. Dearnaley, D. P., Sydes, M. R., Mason, M. D., Stott, M., Powell, C. S., Robinson, A. C., Thompson, P. M., Moffat, L. E., Naylor, S. L., Parmar, M. K.. A double-blind, placebo-controlled, randomized trial of oral sodium clodronate for metastatic prostate cancer (MRC PR05 Trial). J Natl Cancer Inst; Sep 03 2003.
22. Zarogoulidis, K., Boutsikou, E., Zarogoulidis, P., Eleftheriadou, E., Kontakiotis, T., Lithoxopoulou, H., Tzanakakis, G., Kanakis, I., Karamanos, N. K.. The impact of zoledronic acid therapy in survival of lung cancer patients with bone metastasis. Int J Cancer; Oct 01 2009.
23. Wang, Y., Tao, H., Yu, X., Wang, Z., Wang, M.. Clinical significance of zoledronic acid and strontium-89 in patients with asymptomatic bone metastases from non-small-cell lung cancer. Clin Lung Cancer; May 2013.
24. Rosen, L. S., Gordon, D., Tchekmedyian, S., Yanagihara, R., Hirsh, V., Krzakowski, M., Pawlicki, M., de Souza, P., Zheng, M., Urbanowitz, G., Reitsma, D., Seaman, J. J.. Zoledronic acid versus placebo in the treatment of skeletal metastases in patients with lung cancer and other solid tumors: a phase III, double-blind, randomized trial--the Zoledronic Acid Lung Cancer and Other Solid Tumors Study Group. J Clin Oncol; Aug 15 2003.
25. Murakami, H., Yamanaka, T., Seto, T., Sugio, K., Okamoto, I., Sawa, T., Hirashima, T., Takeda, K., Atagi, S., Fukuoka, M., Nakanishi, Y., Nakagawa, K., Yamamoto, N.. Phase II study of zoledronic acid combined with docetaxel for non-small-cell lung cancer: West Japan Oncology Group. Cancer Sci; Aug 2014.
26. Kristensen, B., Ejlertsen, B., Groenvold, M., Hein, S., Loft, H., Mouridsen, H. T.. Oral clodronate in breast cancer patients with bone metastases: a randomized study. J Intern Med; Jul 1999.
27. Kohno, N., Aogi, K., Minami, H., Nakamura, S., Asaga, T., Iino, Y., Watanabe, T., Goessl, C., Ohashi, Y., Takashima, S.. Zoledronic acid significantly reduces skeletal complications compared with placebo in Japanese women with bone metastases from breast cancer: a randomized, placebo-controlled trial. J Clin Oncol; May 20 2005.
28. Kanis, J. A., Powles, T., Paterson, A. H., McCloskey, E. V., Ashley, S.. Clodronate decreases the frequency of skeletal metastases in women with breast cancer. Bone; Dec 1996.
29. James, N., Pirrie, S., Pope, A., Barton, D., Andronis, L., Goranitis, I., Collins, S., McLaren, D., O'Sullivan, J., Parker, C., Porfiri, E., Staffurth, J., Stanley, A., Wylie, J., Beesley, S., Birtle, A., Brown, J., Chakraborti, P., Russell, M., Billingham, L.. TRAPEZE: a randomised controlled trial of the clinical effectiveness and cost-effectiveness of chemotherapy with zoledronic acid, strontium-89, or both, in men with bony metastatic castration-refractory prostate cancer. Health Technol Assess; Jul 2016.
30. Hortobagyi, G. N., Theriault, R. L., Porter, L., Blayney, D., Lipton, A., Sinoff, C., Wheeler, H., Simeone, J. F., Seaman, J., Knight, R. D.. Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. Protocol 19 Aredia Breast Cancer Study Group. N Engl J Med; Dec 12 1996.
31. Heras, P., Kritikos, K., Hatzopoulos, A., Georgopoulou, A. P.. Efficacy of ibandronate for the treatment of skeletal events in patients with metastatic breast cancer. Eur J Cancer Care (Engl); Nov 2009.
32. Body, J. J., Diel, I. J., Lichinitzer, M., Lazarev, A., Pecherstorfer, M., Bell, R., Tripathy, D., Bergstrom, B.. Oral ibandronate reduces the risk of skeletal complications in breast cancer patients with metastatic bone disease: results from two randomised, placebo-controlled phase III studies. Br J Cancer; Mar 22 2004.
33. Body, J. J., Diel, I. J., Lichinitser, M. R., Kreuser, E. D., Dornoff, W., Gorbunova, V. A., Budde, M., Bergstrom, B.. Intravenous ibandronate reduces the incidence of skeletal complications in patients with breast cancer and bone metastases. Ann Oncol; Sep 2003.
34. Pan, Y., Jin, H., Chen, W., Yu, Z., Ye, T., Zheng, Y., Weng, Z., Wang, F.. Docetaxel with or without zoledronic acid for castration-resistant prostate cancer. Int Urol Nephrol; Dec 2014.
35. van Holten-Verzantvoort, A. T., Kroon, H. M., Bijvoet, O. L., Cleton, F. J., Beex, L. V., Blijham, G., Hermans, J., Neijt, J. P., Papapoulos, S. E., Sleeboom, H. P., et al., . Palliative pamidronate treatment in patients with bone metastases from breast cancer. J Clin Oncol; Mar 1993.
36. Ueno, S., Mizokami, A., Fukagai, T., Fujimoto, N., Oh-Oka, H., Kondo, Y., Arai, G., Ide, H., Horie, S., Ueki, O., Kawaguchi, K., Shimamura, M., Orito, M., Ishida, T., Ikeda, D., Namiki, M.. Efficacy of combined androgen blockade with zoledronic acid treatment in prostate cancer with bone metastasis: the ZABTON-PC (zoledronic acid/androgen blockade trial on prostate cancer) study. Anticancer Res; Sep 2013.
37. van Holten-Verzantvoort, A. T., Bijvoet, O. L., Cleton, F. J., Hermans, J., Kroon, H. M., Harinck, H. I., Vermey, P., Elte, J. W., Neijt, J. P., Beex, L. V., et al., . Reduced morbidity from skeletal metastases in breast cancer patients during long-term bisphosphonate (APD) treatment. Lancet; Oct 31 1987.
38. Paterson, A. H., Powles, T. J., Kanis, J. A., McCloskey, E., Hanson, J., Ashley, S.. Double-blind controlled trial of oral clodronate in patients with bone metastases from breast cancer. J Clin Oncol; Jan 1993.
39. Rosen, L. S., Gordon, D. H., Dugan, W.,Jr., Major, P., Eisenberg, P. D., Provencher, L., Kaminski, M., Simeone, J., Seaman, J., Chen, B. L., Coleman, R. E.. Zoledronic acid is superior to pamidronate for the treatment of bone metastases in breast carcinoma patients with at least one osteolytic lesion. Cancer; Jan 01 2004.
40. Smith, M. R., Halabi, S., Ryan, C. J., Hussain, A., Vogelzang, N., Stadler, W., Hauke, R. J., Monk, J. P., Saylor, P., Bhoopalam, N., Saad, F., Sanford, B., Kelly, W. K., Morris, M., Small, E. J.. Randomized controlled trial of early zoledronic acid in men with castration-sensitive prostate cancer and bone metastases: results of CALGB 90202 (alliance). J Clin Oncol; Apr 10 2014.

Forest Plot 5.2.1.1. Complete Pain Relief (Categorical) Bisphosphonates vs. Placebo

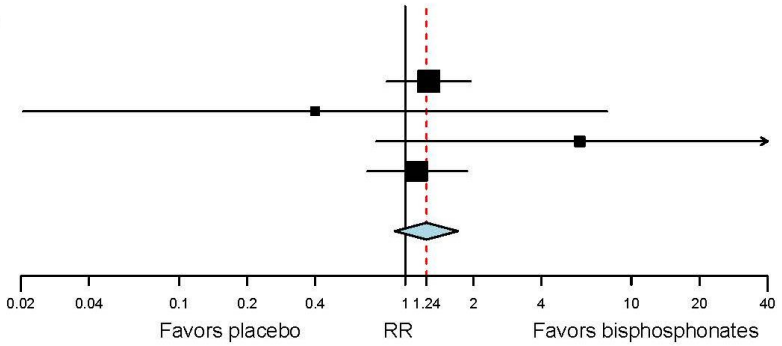
Studies	Estimate (95% C.I.)	Ev/Trt	Ev/Ctrl	Weight
Elomaa 1992 (Clodronate)	1.95 (0.81, 4.72)	10/29	6/34	45.5%
Kylmala 1993 (Clodronate)	1.23 (0.53, 2.84)	10/50	8/49	50.0%
Siris 1983 (Clodronate)	5.00 (0.30, 83.69)	2/5	0/5	4.47%
Overall (I^2=0%, P=0.55)	1.61 (0.89, 2.93)	22/84	14/88	



***Abbreviations**: **CI**: confidence interval; **Ctl**: control (placebo); **Ev**: events (pain relief); **RR**: relative risk (log scale); **Trt**: treatment (bisphosphonate)*

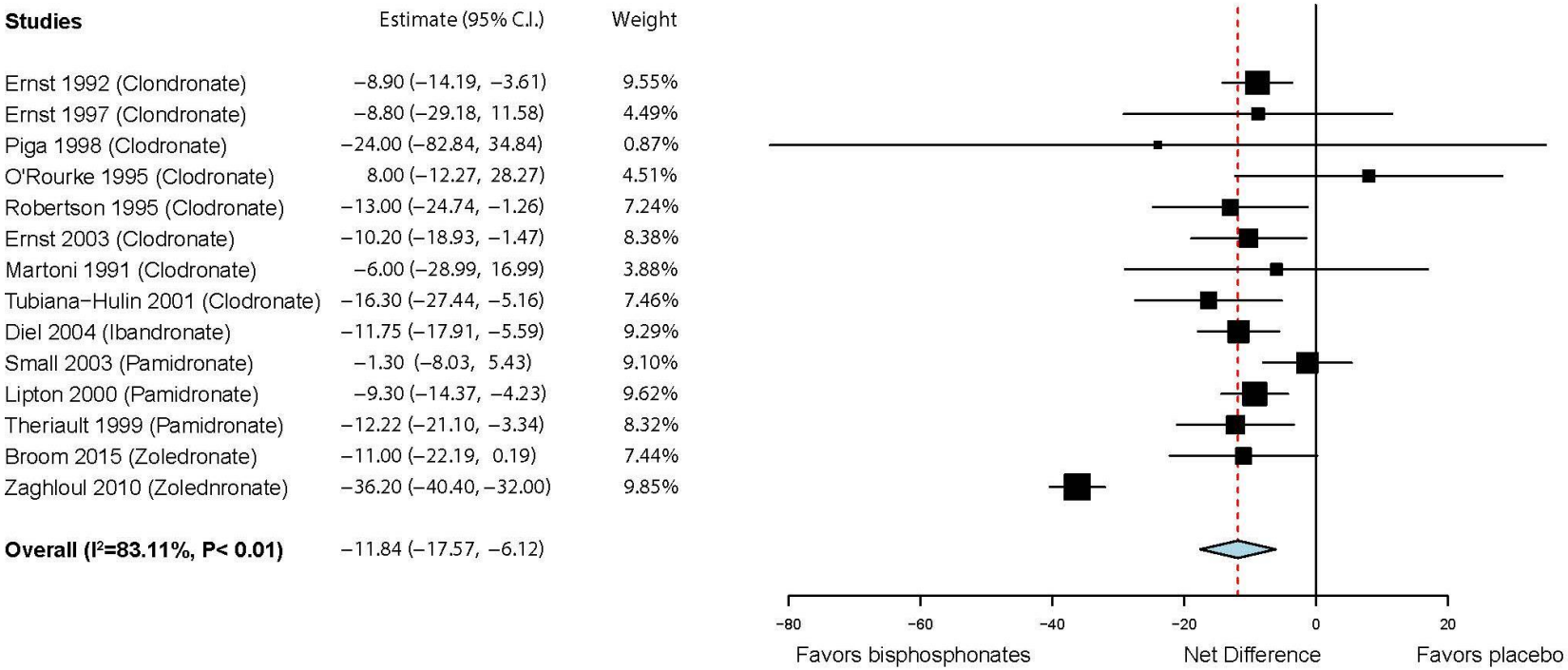
Forest Plot 5.2.1.2. Pain Improvement (Categorical) Bisphosphonates vs. Placebo

Studies	Estimate (95% C.I.)	Ev/Trt	Ev/Ctrl	Weight
Ernst 2003 (Clodronate)	1.27 (0.83, 1.95)	34/104	27/105	56.6%
Smith 1989 (Etidronate)	0.40 (0.02, 7.82)	0/14	2/29	1.16%
Vinholes 1997 (Pamidronate)	5.91 (0.75, 46.86)	5/22	1/26	2.40%
Meulenbeld 2012 (Risendronate)	1.13 (0.68, 1.88)	22/70	20/72	39.8%
Overall (I^2=0%, P=0.41)	1.24 (0.90, 1.71)	61/210	50/232	



***Abbreviations**: **CI**: confidence interval; **Ctl**: control (placebo); **Ev**: events (pain improvement); **RR**: relative risk (log scale); **Trt**: treatment (bisphosphonate)*

Forest Plot 5.2.1.3. Pain Relief (Continuous) Bisphosphonates vs. Placebo

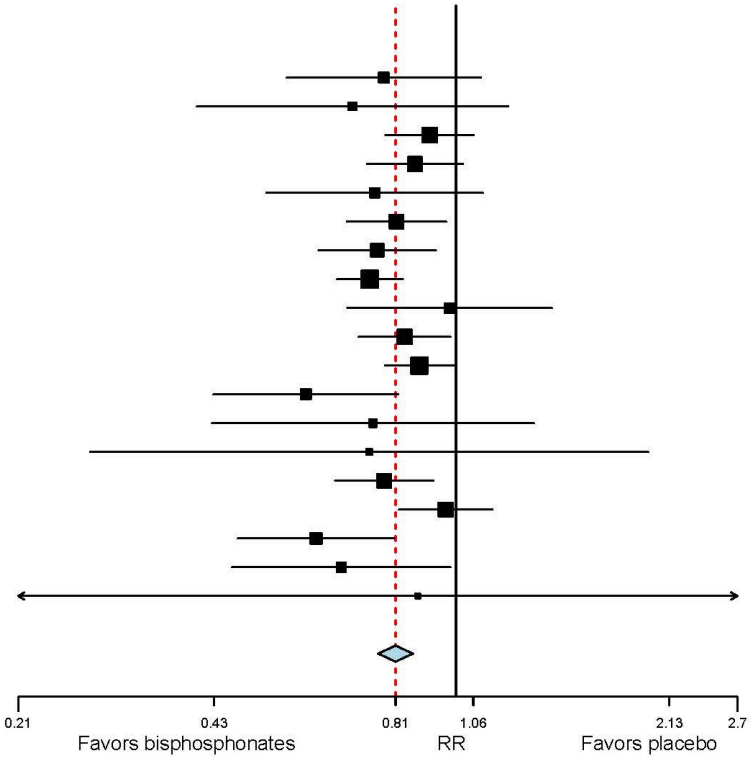


***Abbreviation**: **CI**: confidence interval.*

Scores from individual studies have been transformed to a uniform 0-100 scale (100 = worst).

Forest Plot 5.2.1.4. Skeletal-Related Events (Any) Bisphosphonates vs. Placebo

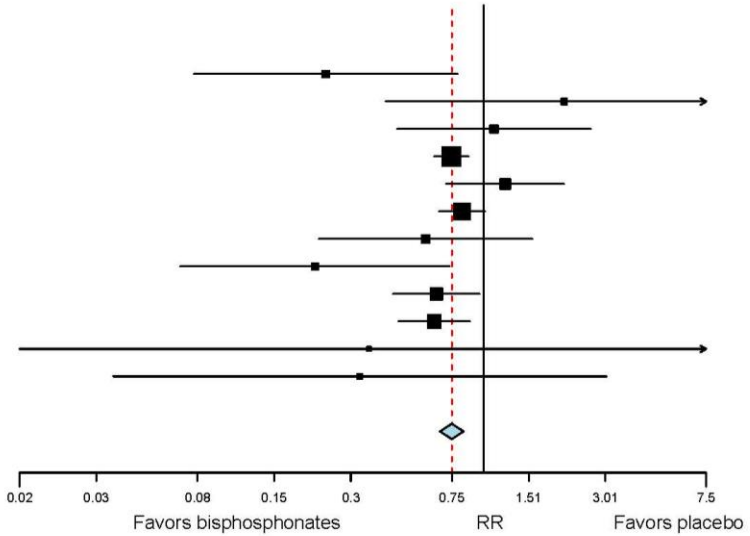
Studies	Estimate (95% C.I.)	Ev/Trt	Ev/Ctrl	Weight
Kanis 1996 (Clodronate)	0.77 (0.55, 1.09)	29/66	38/67	2.78%
Kristensen 1999 (Clodronate)	0.69 (0.40, 1.20)	14/49	21/51	1.17%
Body 2003 (Ibandronate)	0.91 (0.78, 1.07)	174/308	98/158	9.04%
Body 2004 (Ibandronate)	0.87 (0.73, 1.03)	130/287	145/277	8.19%
Heras 2009 (Ibandronate)	0.75 (0.51, 1.10)	27/75	36/75	2.29%
Tripathy 2004 (Ibandronate)	0.81 (0.68, 0.97)	144/292	87/143	7.84%
Hortobagyi 1996 (Pamidronate)	0.76 (0.62, 0.93)	79/185	110/195	6.24%
Lipton 2000 (Pamidronate)	0.74 (0.66, 0.83)	194/367	263/367	12.3%
Small 2003 (Pamidronate)	0.98 (0.68, 1.40)	42/169	46/181	2.53%
Theriault 1999 (Pamidronate)	0.83 (0.71, 0.98)	102/182	127/189	8.63%
James 2016 (Zolendronate)	0.88 (0.78, 0.99)	203/376	234/381	11.7%
Kohno 2005 (Zolendronate)	0.59 (0.42, 0.82)	35/114	59/113	3.02%
Murakami 2014 (Zolendronate)	0.75 (0.42, 1.32)	14/48	18/46	1.10%
Pan 2014 (Zolendronate)	0.74 (0.27, 1.97)	6/53	8/52	0.38%
Rosen 2003 (Zolendronate)	0.78 (0.65, 0.92)	190/523	117/250	7.92%
Smith 2014 (Zoledronate)	0.96 (0.82, 1.14)	147/323	152/322	8.41%
Wang 2013 (Zolendronate)	0.61 (0.46, 0.80)	25/45	41/45	4.01%
Zaghloul 2010 (Zolendronate)	0.67 (0.45, 0.98)	12/20	18/20	2.25%
Zarogoulidis 2009 (Zolendronate)	0.87 (0.20, 3.76)	4/87	3/57	0.17%
Overall (I^2=27.2%, P=0.22)	0.81 (0.76, 0.86)	1571/3569	1621/2989	



***Abbreviations**: **CI**: confidence interval; **Ctl**: control (placebo); **Ev**: events (skeletal-related events); **RR**: relative risk (log scale); **Trt**: treatment (bisphosphonate).*

Forest Plot 5.2.1.5. Skeletal-Related Events (Fractures) Bisphosphonates vs. Placebo

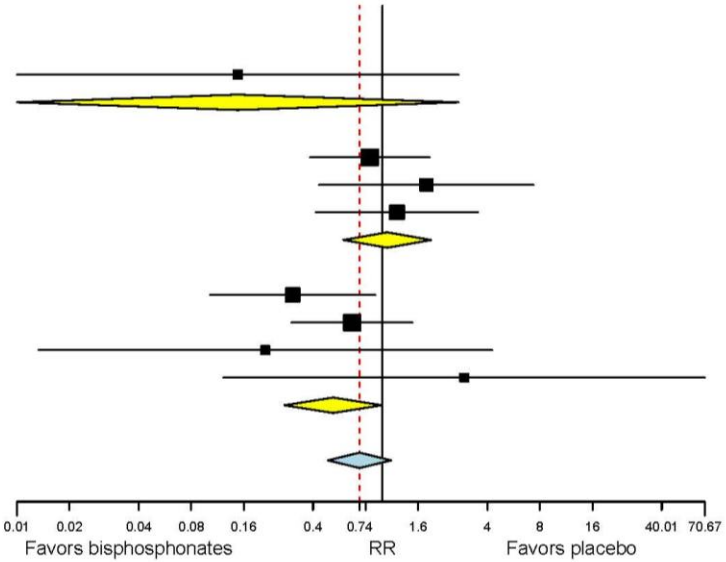
Studies	Estimate (95% C.I.)	Ev/Trt	Ev/Ctrl	Weight
Kristensen 1999 (Clodronate)	0.24 (0.07, 0.79)	3/49	13/51	0.80%
Robertson 1995 (Clodronate)	2.07 (0.41, 10.41)	4/27	2/28	0.44%
Diel 2004 (Ibandronate)	1.10 (0.46, 2.64)	15/308	7/158	1.48%
Lipton 2000 (Pamidronate)	0.75 (0.64, 0.87)	148/367	198/367	46.5%
Small 2003 (Pamidronate)	1.22 (0.71, 2.07)	25/169	22/181	4.00%
Theriault 1999 (Pamidronate)	0.82 (0.67, 1.02)	81/182	102/189	26.0%
van Holten−Verzantvoort 1993 (Pamidronate)	0.59 (0.23, 1.55)	6/81	10/80	1.20%
van Holten−Verzantvoort 1987 (Pamidronate)	0.22 (0.06, 0.74)	3/70	12/61	0.80%
Kohno 2005 (Zolendronate)	0.65 (0.44, 0.96)	29/114	44/113	7.47%
Rosen 2003 (Zolendronate)	0.64 (0.46, 0.88)	71/523	53/250	10.9%
Ueno 2013 (Zolendronate)	0.36 (0.02, 8.39)	0/29	1/31	0.11%
Pan 2014 (Zolendronate)	0.33 (0.04, 3.04)	1/53	3/52	0.23%
Overall (I^2=0%, P=0.14)	0.75 (0.67, 0.84)	386/1972	467/1561	



***Abbreviations**: **CI**: confidence interval; **Ctl**: control (placebo); **Ev**: events (skeletal-related events); **RR**: relative risk (log scale); **Trt**: treatment (bisphosphonate).*

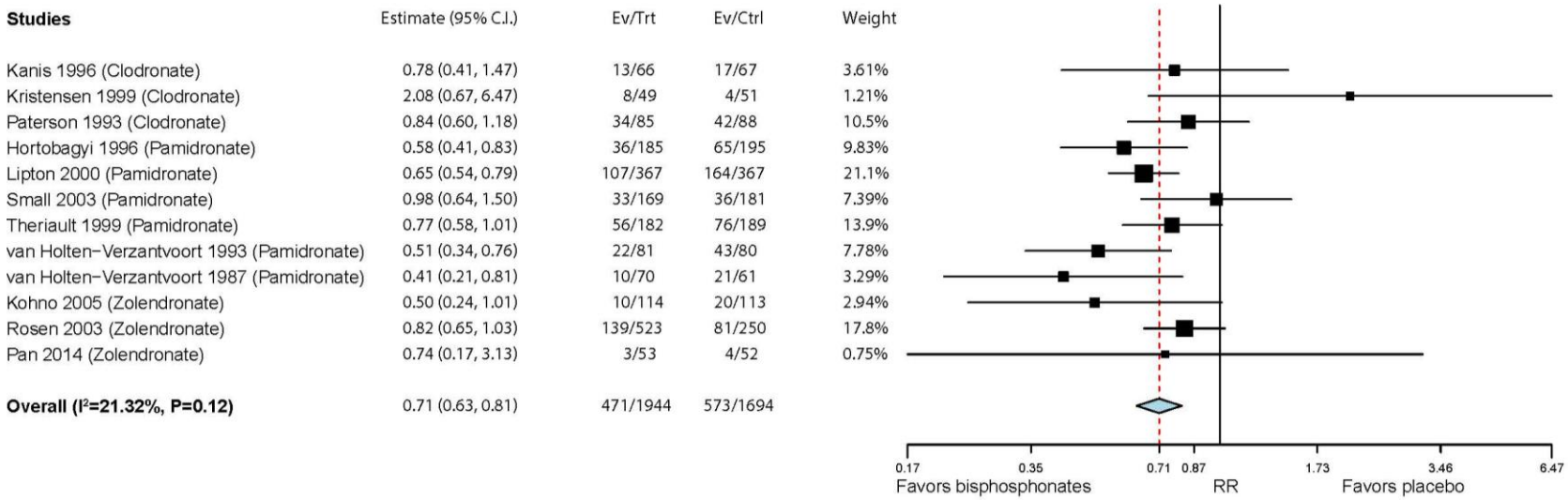
Forest Plot 5.2.1.6. Skeletal-Related Events (Spinal Cord Compressions) Bisphosphonates vs. Placebo

Studies	Estimate (95% C.I.)	Ev/Trt	Ev/Ctrl	Weight
Robertson 1995 (Clodronate)	0.15 (0.01, 2.74)	0/27	3/28	2.06%
Subgroup Clodronate (I^2=NA, P=NA)	0.15 (0.01, 2.74)	0/27	3/28	
Lipton 2000 (Pamidronate)	0.85 (0.38, 1.86)	11/367	13/367	28.1%
Small 2003 (Pamidronate)	1.79 (0.43, 7.35)	5/169	3/181	8.73%
Theriault 1999 (Pamidronate)	1.21 (0.42, 3.54)	7/182	6/189	15.3%
Subgroup Pamidronate (I^2=0%, P=0.64)	1.07 (0.60, 1.90)	23/718	22/737	
Kohno 2005 (Zolendronate)	0.30 (0.10, 0.91)	4/114	13/113	14.7%
Rosen 2003 (Zolendronate)	0.67 (0.30, 1.49)	14/523	10/250	27.5%
Ueno 2013 (Zolendronate)	0.21 (0.01, 4.26)	0/29	2/31	1.95%
Pan 2014 (Zolendronate)	2.94 (0.12, 70.67)	1/53	0/52	1.70%
Subgroup Zolendronate (I^2=3.39%, P=0.43)	0.52 (0.27, 0.99)	19/719	25/446	
Overall (I^2=0%, P=0.37)	0.74 (0.49, 1.12)	42/1464	50/1211	



***Abbreviations**: **CI**: confidence interval; **Ctl**: control (placebo); **Ev**: events (skeletal-related events); **RR**: relative risk (log scale); **Trt**: treatment (bisphosphonate).*

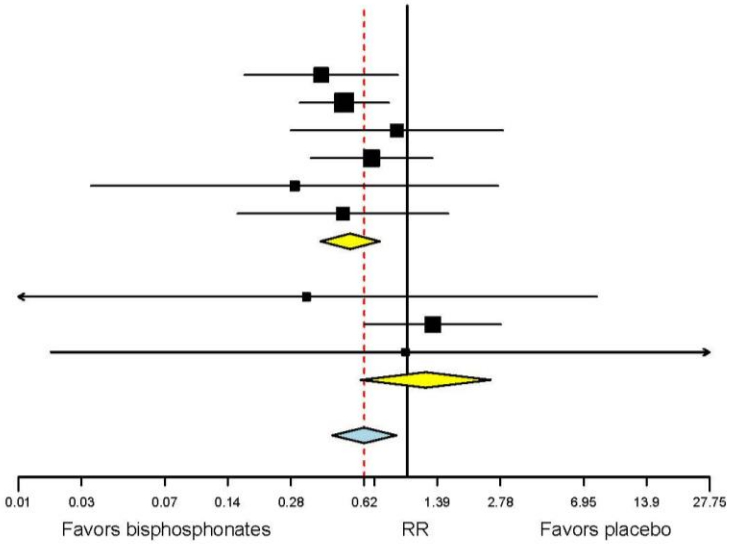
Forest Plot 5.2.1.7. Skeletal-Related Events (Bone Radiotherapy) Bisphosphonates vs. Placebo



***Abbreviations**: **CI**: confidence interval; **Ctl**: control (placebo); **Ev**: events (skeletal-related events); **RR**: relative risk (log scale); **Trt**: treatment (bisphosphonate).*

Forest Plot 5.2.1.8. Skeletal-Related Events (Bone Surgery) Bisphosphonates vs. Placebo

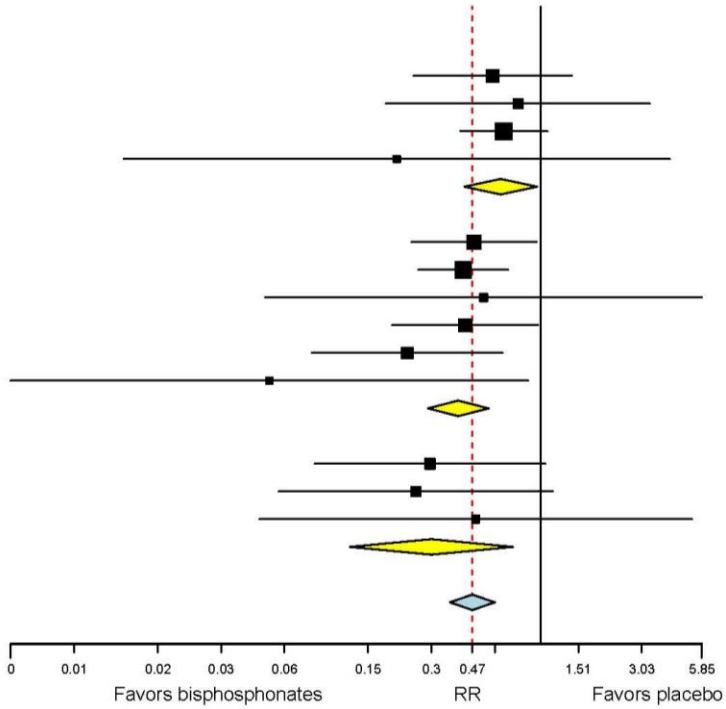
Studies	Estimate (95% C.I.)	Ev/Trt	Ev/Ctrl	Weight
Hortobagyi 1996 (Pamidronate)	0.39 (0.17, 0.90)	7/185	19/195	13.9%
Lipton 2000 (Pamidronate)	0.50 (0.31, 0.82)	22/367	44/367	29.2%
Small 2003 (Pamidronate)	0.89 (0.28, 2.87)	5/169	6/181	8.00%
Theriault 1999 (Pamidronate)	0.67 (0.35, 1.32)	13/182	20/189	19.7%
van Holten−Verzantvoort 1993 (Pamidronate)	0.29 (0.03, 2.72)	1/70	3/61	2.39%
van Holten−Verzantvoort 1987 (Pamidronate)	0.49 (0.15, 1.57)	4/81	8/80	8.11%
Subgroup Pamidronate (I^2=0%, P=0.83)	0.53 (0.39, 0.74)	52/1054	100/1073	
Kohno 2005 (Zolendronate)	0.33 (0.01, 8.03)	0/114	1/113	1.20%
Rosen 2003 (Zolendronate)	1.33 (0.63, 2.80)	25/523	9/250	16.7%
Pan 2014 (Zolendronate)	0.98 (0.02, 48.56)	0/53	0/52	0.80%
Subgroup Zolendronate (I^2=0%, P=0.70)	1.23 (0.60, 2.51)	25/690	10/415	
Overall (I^2=16.96%, P=0.52)	0.62 (0.44, 0.89)	77/1744	110/1488	



***Abbreviations**: **CI**: confidence interval; **Ctl**: control (placebo); **Ev**: events (skeletal-related events); **RR**: relative risk (log scale); **Trt**: treatment (bisphosphonate).*

Forest Plot 5.2.1.9. Skeletal-Related Events (Hypercalcemia) Bisphosphonates vs. Placebo

Studies	Estimate (95% C.I.)	Ev/Trt	Ev/Ctrl	Weight
Kanis 1996 (Clodronate)	0.59 (0.25, 1.41)	7/66	12/67	7.98%
Kristensen 1999 (Clodronate)	0.78 (0.18, 3.31)	3/49	4/51	2.88%
Paterson 1993 (Clodronate)	0.67 (0.41, 1.08)	20/85	31/88	26.5%
Robertson 1995 (Clodronate)	0.21 (0.01, 4.13)	0/27	2/28	0.67%
Subgroup Clondronate (I^2=0%, P=0.88)	0.65 (0.43, 0.96)	30/227	49/234	
Hortobagyi 1996 (Pamidronate)	0.48 (0.24, 0.96)	11/185	24/195	12.8%
Lipton 2000 (Pamidronate)	0.43 (0.26, 0.70)	21/367	49/367	25.0%
Small 2003 (Pamidronate)	0.54 (0.05, 5.85)	1/169	2/181	1.05%
Theriault 1999 (Pamidronate)	0.44 (0.20, 0.97)	8/182	19/189	9.38%
van Holten−Verzantvoort 1993 (Pamidronate)	0.23 (0.08, 0.66)	4/81	17/80	5.51%
van Holten−Verzantvoort 1987 (Pamidronate)	0.05 (0.00, 0.87)	0/70	8/61	0.75%
Subgroup Pamidronate (I^2=0%, P=0.62)	0.41 (0.29, 0.57)	45/1054	119/1073	
Kohno 2005 (Zolendronate)	0.30 (0.08, 1.05)	3/114	10/113	3.76%
Murakami 2014 (Zolendronate)	0.26 (0.06, 1.14)	2/49	8/50	2.68%
Pan 2014 (Zolendronate)	0.49 (0.05, 5.25)	1/53	2/52	1.07%
Subgroup Zolendronate (I^2=0%, P=0.90)	0.30 (0.12, 0.74)	6/216	20/215	
Overall (I^2=0%, P=0.74)	0.47 (0.37, 0.60)	81/1497	188/1522	



***Abbreviations**: **CI**: confidence interval; **Ctl**: control (placebo); **Ev**: events (skeletal-related events); **RR**: relative risk (log scale); **Trt**: treatment (bisphosphonate).*

<table>
<tr><td colspan="3">Evidence-to-Decision table 5.2.1</td></tr>
<tr><td colspan="3">In adults (including older persons) and adolescents with bone metastases, what is the evidence for the use of bisphosphonates compared no treatment in order to prevent and treat pain?</td></tr>
<tr><td>POPULATION:</td><td>Adults (including older persons) and adolescents with cancer-related pain</td><td rowspan="6">Background:

Bone pain is the most common type of pain from cancer and is present in approximately one out of three patients with bone metastases.[129]. The pain is commonly a mixture of background pain and incident/episodic pain, which is commonly associated with weight bearing or movement.[130] Bone metastases can weaken bone sufficiently to greatly increase patients' risk of fracture.

Bisphosphonates inhibit osteoclasts, and their use in cancer patients prevents the elevated bone resorption common in metastatic bone disease. They thus reduce complications or skeletal related events (SREs), and reduce bone pain and analgesic requirements.[131,132]

Current WHO recommendation:

• The WHO 1996 cancer pain relief guidelines do not address the use of bisphosphonates. There are no GRC approved guidelines on the use of bisphosphonates for pain relief.
• Zoledronic acid was added to the WHO Model list of essential medicines for adults in 2017.</td></tr>
<tr><td>INTERVENTION:</td><td>Bisphosphonates</td></tr>
<tr><td>COMPARISON:</td><td>Placebo (no treatment)</td></tr>
<tr><td>MAIN OUTCOMES:</td><td>• Pain relief
• Pain relief speed
• Pain relief maintenance
• Quality of life (QoL)
• Functional outcomes
• Skeletal-related events
• Osteonecrosis of the jaw (adverse event)</td></tr>
<tr><td>STRATIFICATIONS:</td><td>• Age (adults, older persons, adolescents, children)
• History of substance abuse
• Refractory pain</td></tr>
<tr><td>SETTING:</td><td>All</td></tr>
<tr><td>PERSPECTIVE:</td><td>Population</td></tr>
</table>

	CRITERIA	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** Yes	**Research Evidence** None **Additional considerations** Bisphosphonates are commonly used in for pain relief in clinical practice. Yet WHO does not have guidance on their use.

BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Yes No Uncertain Yes ☐ ☐	• **Forty randomized controlled trials** compared bisphosphonates to placebo. Most trial participants had either breast or prostate cancer. Fifteen of the trials were restricted to people (women or men) with breast cancer (or included mostly people with breast cancer). Ten trials were restricted to men with prostate cancer. The third most common cancer across studies was lung cancer. Thirteen trials evaluated clodronate, nine zolendronate, five each ibandronate and pamidronate, and one each etidronate and risendronate. **BENEFITS and HARMS** • **Three trials** provided **moderate strength of evidence favoring use of bisphosphonates to provide bone pain relief;** RR = 1.61 (95% CI 0.89, 2.93) **Four trials** provided **moderate strength of evidence favoring use of bisphosphonates to improve bone pain;** RR = 1.24 (95% CI 0.90, 1.71). **Fourteen trials** provided **moderate strength of evidence** when evaluating pain on continuous scales (which were each converted to a 100 point scale, with 100 = worst pain). The studies, overall, **indicated decrease in pain with bisphosphonates**, with an overall net difference of -11.8 (95% CI -17.6, -6.1). • **No trial** reported on **pain relief speed**. • **One trial** provided **low strength of evidence** suggesting **no difference in duration of pain relief** between risendronate and placebo in people with prostate cancer (HR = 1.27; 95% CI 0.84, 1.92), nominally favoring placebo (3.4 month median duration with risendronate, 5.5 months with placebo). • **Five studies** provide **moderate strength of evidence** that **bisphosphonates improve QoL compared with placebo.** One provided moderate strength of evidence of reduced and delayed deterioration in quality of life with clodronate (RR = 0.81; 95% CI 0.67, 0.99 and HR = 0.71; 95% CI 0.56, 0.92). The five trials, overall, provided very low strength of evidence of no significant difference in changes in quality of life scores measured on a variety of scales (summary net difference on a 0 to 100 [best] scale = 8; 95% CI -6, 22). • **Two trials** provided **very low to low strength of evidence in functional outcomes favoring bisphosphonates**. One trial each found net differences (all transformed to 100 point scale where 100 = best score) in ECOG performance status of -7.7 (95% CI -17.0, 1.7), in FACT-P physical well-being of 1.4 (95% CI 0.5, 3.3), in FACT-P social well-being of 1.8 (95% CI 1.0, 2.6), and in FACT-P functional well-being of 1.8 (95% CI 0.6, 2.9). • **Twenty trials** provided **moderate strength of evidence** that **bisphosphonates reduce the risk of any skeletal-related events;** 18 of these trials yielded a summary RR of 0.81 (95% CI 0.76, 0.86). Six trials provided moderate strength of evidence of that reported hazard ratios for time to first skeletal-related event (any) in comparisons of zolendronate (4 studies) or ibandronate (2 studies) found a statistically significant benefit of bisphosphonates over placebo (HR = 0.71; 95% CI 0.61, 0.84). • **Twelve trials** provided **moderate strength of evidence** of **reduction in risk of fracture with bisphosphonates** (RR = 0.75; 95% CI 0.67, 0.84).

		• **Eight trials** provided **moderate strength of evidence** nominally **favoring bisphosphonates to reduce the risk of spinal cord compressions** (RR = 0.74; 95% CI 0.49, 1.12). The three zolendronate trials together found a statistically significant reduction in risk of spinal cord compression (RR = 0.52; 95% CI 0.27, 0.99), but this result was not significantly different than the nonsignificant summary of the pamidronate studies (RR = 1.07; 95% CI 0.60, 1.90; P=0.72 between studies of different medications). • **Twelve trials** provided **moderate strength of evidence** that the risk of **bone radiotherapy was significantly reduced risk with bisphosphonates** (RR = 0.71; 95% CI 0.63, 0.81). • **Nine trials** provided **moderate strength of evidence** of a **significantly reduced risk of bone surgeries with bisphosphonates** (RR = 0.62; 95% CI 0.44, 0.89). A significantly greater risk reduction was found in the four studies of pamidronate (RR = 0.53; 95% CI 0.39, 0.74) than the two studies of zolendronate (RR = 1.23; 95% CI 0.60, 2.51; P=0.042 between studies of different medications). • **Thirteen trials** provided **moderate strength of evidence** of **reduced risk of hypercalcemia with bisphosphonates compared to placebo** (RR = 0.47; 95% CI 0.37, 0.60). The trials of zolendronate (RR = 0.30; 95% CI 0.12, 0.74) and pamidronate (RR = 0.41; 95% CI 0.29, 0.57) showed a nominally stronger effect on hypercalcemia than trials of clodronate (RR = 0.65; 95% CI 0.43, 0.96), but the differences among studies of different medications were not statistically significant (P=0.072). • **Four trials** provided **low strength of evidence** and **reported on the risk of osteonecrosis of the jaw.** Across the trials, there were no occurrences of this adverse event with either bisphosphonates (N=460) or placebo (N=450). **STRATIFICATIONS** • Studies conducted in adults with a wide age range, without stratification into adolescent, non-older persons, and older persons. • Studies provide no data regarding history of substance abuse. • Studies provide no data regarading refractory pain. **SUMMARY** Bisphosphonantes probably reduce bone pain and the risk of skeletal-related events and improve QoL. They may improve functional outcomes, but may make little or no difference to duration of pain relief. Rates of osteonecrosis of the jaw may be rare with bisphosphonates.

ACCEPTABILITY & PREFERENCES	**Is there important uncertainty or variability about how much people value the options?** Major variability [ ] Minor variability [Yes] Uncertain [ ] **Is the option acceptable to key stakeholders?** Yes No Uncertain [Yes] [ ] [ ]	**<u>Research evidence</u>** None presented. **<u>Additional considerations</u>** The GDG believed that most patients would prefer bisphosphonates over placebo. The GDG deemed bisphosphonates acceptable to clinicians.

FEASIBILITY ./ RESOURCE USE

How large are the resource requirements?

Major	Minor	Uncertai
Yes		

Is the option feasible to implement?

Yes	No	Uncertain
Yes		

Medication	Price (USD) per vial or tablet		
	International Medical Products Price Guide, Median price	Drugs.com	Pharmacychecker.com
Zoledronate (4mg/5ml IV solution, 5ml)	$ 23.4501	$ 45.52	-
Clodronate (800mg)	NA	NA	$ 3.87
Ibandronate (3mg/3mL IV solution, 3ml)	NA	$ 218.56	-
Pamidronate (3mg/ml IV solution, 10ml)	NA	$ 20.16	-
Etidronate (200mg oral tablet)	NA	$ 3.17	-
Risendronate (35mg tablet)	NA	$ 38.75	-

- The GDG recognized the high costs of bisphosphonate medications.
- Almost all the RCTs were conducted with intermittent intravenous administration. Using this method could be considered as a potential feasibility issue according to the GDG.

Would the option improve equity in health?

Yes	No	Uncertai
		Yes

Research Evidence

The use of bisphosphonates in populations of older women with osteoporosis and in breast cancer patients with bone metastases has been deemed cost-saving or cost effective (depending on population) in a number of high income countries .[133-135] It remains to be seen whether these savings would apply to lower income settings.

Additional considerations

Bisphosphonates are expensive throughout the world. In most settings, their use is often prohibitively expensive.

Combining these considerations, the GDG felt that equity could be affected in either direction, and therefore opted for uncertainty in this regard.

Recommendation	**Current recommendation:** None **New (draft) recommendation:** In adults (including older persons) and adolescents with bone metastases, a bisphosphonate should be used to prevent and treat bone pain.
Strength of Recommendation	**Strong**
Quality of Evidence	➢ **MODERATE** [Pain (critical) = moderate Pain reduction maintenance (critical) = low QoL (critical) = very low (continuous), moderate (categorical) Skeletal-related events (important) = moderate (any, fracture, spinal cord compression, radiotherapy, bone surgery, hypercalcemia) Functional outcomes (important) = low, very low (physical, social, functional) Osteonecrosis of jaw (important) = low others omitted for no data or indeterminate findings]
Justification	The GDG felt that the balance of effect fell strongly in favour of prescribing bisphosphonates to appropriate populations. Osteonecrosis of the mandible, considered a serious adverse event, was deemed sufficiently rare (no cases were observed in the eligible trials) that the expected benefits outweighed the risks of harm. Consideration was given to the issue that administration of the bisphosphonates should be IV, but this was not deemed to be a significant enough barrier to administration that the strength of the recommendation should be attenuated.
Subgroup considerations	
Implementation considerations [incl. M&E]	
Research priorities	

5.2.2. Comparisons of Bisphosphonates

Seven eligible studies compared different bisphosphonates (see Evidence Profile 5.2.2) in patients with various cancers with bone metastases—mostly breast, prostate, and non-small cell lung cancer [127,136];Francini, 2011 #235;Choudhury, 2011 #236;Wang, 2013 #237;Barrett-Lee, 2014 #238;von Au, 2016 #239}. The studies evaluated clodronate, ibandronate, pamidronate, and zoledronate. Study participants were generally older, with study mean ages ranging from 53 to 73 years old. As will be shown, the evidence is relatively sparse, with only seven studies evaluating four bisphosphonates. There are six possible pairwise comparisons (e.g., clodronate vs. ibandronate, clodronate vs. pamidronate, …). With more studies reporting on the same outcomes, network meta-analysis may be feasible in the future. Given these limitations, the evidence is of low or very low strength, as will be elaborated. For these reasons, there are not six separate evidence profiles (for each pairwise comparison) and no relative effects (e.g., RR) for these pairwise comparisons. Instead, absolute event rates (or within-arm changes) are provided for each of the four medications.

With only two or three studies evaluating pain control, there is low strength of evidence of no differences in relief of pain or mean changes in pain scores across the different bisphosphonates. From one study, pain relief on ibandronate (6%) was less common than on other bisphosphonates (15-26% in one or two studies for each medication). Changes in pain (as a continuous measure from 0 to 100 [worst]) were similar for each of the four bisphosphonates (-3.3 to -5.0). The studies did not report on speed of pain relief. Two studies provided very low strength of evidence regarding duration of pain relief. One study found no difference in average duration of pain relief in patients with a variety of cancers (about half with lung cancer) between ibandronate (5.5 months) and pamidronate (5.2 months).[137] One study reported that in patients with prostate cancer those taking clodronate had longer duration of pain relief (13 months) than those taking ~~zolendronate~~zoledronate (9 months, P=0.03).[138]

Six studies reported on skeletal-related events. However, the studies had serious methodological limitations, sparsely reported on any give comparison across the four bisphosphonates, and were generally small resulting in imprecision. Thus, there is very low strength of evidence overall regarding skeletal-related events. Broadly similar percentages of people had any skeletal-related event across bisphosphonates (18-26%, no data on pamidronate). Within studies, fracture rates were mostly similar between bisphosphonates, except in one study of people with breast cancer in which 16% of those taking clodronate had fractures compared with 7% taking pamidronate (P=0.03). Three studies found no significant differences in rates of spinal cord compression across bisphosphonates. Two studies no significant differences in rates of bone radiotherapy across bisphosphonates. Three studies found no significant differences in rates of bone surgery across bisphosphonates.

Three studies reported on rates of hypercalcemia across bisphosphonates. Two of these found no differences in risk of hypercalcemia between ibandronate (10.7%) and ~~zolendronate~~zoledronate (9.3%) in one study, and between clodronate (2.9%) and ~~zolendronate~~zoledronate (1.4%) in the other. The third study, however, reported the hypercalcemia rate in the ~~zolendronate~~zoledronate group (28%%) was lower than with ibandronate (45%; RR = 0.64; 95% CI 0.39, 1.03) or with pamidronate (50%; RR = 0.57; 95% CI 0.35, 0.91). Three studies reported rare rates of osteonecrosis of the jaw for clodronate (1.5%), ibandronate (0.7%), and ~~zolendronate~~zoledronate (1.2), providing low strength of evidence.

Evidence Profile 5.2.2. Comparison of Bisphosphonates

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Clodronate Ibandronate**	**Pamidronate Zoledronate**	**Clodronate Ibandronate**	**Pamidronate Zoledronate**		
Pain relief (categorical) (follow up: range 6 months to 2 years)												
2 [1,2]	RCT	serious [A]	not serious	not serious	not serious	sparse [B]	C 212 (1 study) I 65 (1 study)	P 171 (2 studies) Z 60 (1 study)	C 56/212 (26%) I 4/65 (6%)	P 40/171 (22% [C]) Z 9/60 (15%)	Low	CRITICAL
Pain relief (continuous) (follow up: range 6 months to 3 years; assessed with: BPI, VAS; Scale: 0 to 100 [worst]*)												
3 [2,3,4]	RCT	serious [D]	not serious	not serious	not serious	sparse [B]	C 68 (1 study) I 731 (2 studies)	P 62 (1 study) Z 774 (3 studies)	**Difference:** C -3.6 (-4.5, -2.7) I -3.3 (-4.2, -2.4)	**Difference:** P -4.2 (-4.9, -3.5) Z -5.0 (-5.5, -4.4)	Low	CRITICAL
Pain relief speed												
0									not estimable	not estimable		IMPORTANT
Pain reduction maintenance (follow up: range 6 months to 3 years)												
2 [2,3]	RCT	serious [D]	not serious	not serious	serious [E]	sparse [B]	C 68 (1 study) I 65 (1 study)	P 62 (1 study) Z 129 (2 studies)	**Difference:** C 13 (nd) mo I 5.5 (4.9, 6.0) mo	**Difference:** P 5.2 (4.7, 5.7) mo Z 7.4 (4.1, 10.6) [F] mo	Very Low	CRITICAL
Skeletal-related events, any (follow up: range 3 months to 3 year)												
2 [3,6]	RCT	serious [D]	not serious	not serious	serious [G]	sparse [B]	C 68 (1 study) I 27 (1 study)	P 0 Z 95 (2 studies)	C 14/68 (21%) I 7/27 (26%)	P nd Z 71/95 (18% [C])	Very Low	IMPORTANT
Skeletal-related events, fracture (follow up: range 3 months to 3 year)												
4 [1,2,3,4]	RCT	serious [D]	not serious	not serious	serious [G]	sparse [B]	C 280 (2 studies) I 796 (2 studies)	P 171 (2 studies) Z 826 (3 studies)	C 38/280 (11% [C]) I 119/769 (21% [C])	P 37/171 (27% [C]) [H] Z 109/826 (10% [C])	Very Low	IMPORTANT
Skeletal-related events, spinal cord compression (follow up: range 3 months to 3 year)												
3 [2,3,4]	RCT	serious [D]	not serious	not serious	serious [G]	sparse [B]	C 68 (1 study) I 769 (2 studies)	P 62 (1 study) Z 826 (3 studies)	C 1/68 (1.5%) [I] I 23/769 (2.9% [C])	P 7/62 (11%) Z 27/826 (3.1% [C])	Very Low	IMPORTANT
Skeletal-related events, bone radiation (follow up: range 3 months to 3 year)												
2 [3,4]	RCT	serious [D]	not serious	not serious	serious [G]	sparse [B]	C 68 (1 study) I 704 (1 study)	P 0 Z 766 (2 studies)	C 7/68 (10%) [J] I 210/704 (30%)	P nd Z 194/766 (18% [C])	Very Low	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clodronate Ibandronate	Pamidronate Zoledronate	Clodronate Ibandronate	Pamidronate Zoledronate		
Skeletal-related events, bone surgery (follow up: range 3 months to 3 year)												
3 [2,3,4]	RCT	serious [D]	not serious	not serious	serious [G]	sparse [B]	C 68 (1 study) I 769 (2 studies)	P 62 (1 study) Z 826 (3 studies)	C 0/68 (0%) [I] I 45/769 (5.9% [C])	P 4/62 (6.5%) Z 35/826 (3.8% [C])	Very Low	IMPORTANT
Skeletal-related events, hypercalcemia (follow up: range 3 months to 3 year)												
3 [2,3,4]	RCT	serious [D]	not serious	not serious	serious [G]	sparse [B]	C 68 (1 study) I 769 (2 studies)	P 62 (1 study) Z 826 (3 studies)	C 2/68 (2.9%) [I] I 104/769 (27% [C])	P 31/62 (50%) [K] Z 83/826 (12% [C])	Very Low	IMPORTANT
Quality of life												
0									not estimable	not estimable		CRITICAL
Functional outcomes												
0									not estimable	not estimable		IMPORTANT
Adverse events: Osteonecrosis of jaw												
3 [3,4,6]	RCT	serious [D]	not serious	not serious	very serious [L]	none	C 68 (1 study) I 731 (2 studies)	P 0 Z 792 (3 studies)	C 1/68 (1.5%) [M] I 5/731 (0.7% [C]) [M]	P nd Z 10/792 (1.2% [C]) [M]	Very Low	IMPORTANT

***Abbreviations**: **C:** clodronate; **CI**: confidence interval; **GI:** gastrointestinal; **I:** ibandronate; **mo**: months; **N/A**: not applicable; **nd**: no data; **NS**: not statistically significant; **P**: pamidronate; **RCT**: randomized controlled trial(s); **SRE**: skeletal-related event;*
***Z**: zoledronate.*

Explanations

A. Incomplete data reporting.
B. Sparse direct comparisons.
C. Meta-analyzed value.
D. Lack of blinding, incomplete data reporting.
E. Incomplete variance data.
F. Meta-analyzed value. Assumes standard deviation is the same in the study that did not report variance data as the study that did.
G. Small sample sizes for most comparisons.
H. von Au et al. reported significantly fewer fractures with pamidronate (7%) than clodronate (16%; P=0.033), but Choudhury et al. reported more (but statistically similar) fractures with pamidronate (47%) than ibandronate (29%) or ~~zolendronate~~zoledronate (25%).
I. In the same study, the rate in the zole~~n~~dro~~a~~nate group was 1/69 (1.4%), which was not significantly different.
J. In the same study, the rate in the zole~~n~~dro~~a~~nate group was 6/69(8.7%), which was not significantly different.
K. In the same study, the rate in the ibandronate group was 29/65 (45%), which was not significantly different (RR = 0.64; 95% CI 0.39, 1.03), but the rate in the ~~zolendronate~~zoledronate group was 17/60 (28%), which was significantly lower (RR = 0.57; 95% CI 0.35, 0.91).
L. Imprecise estimates for each comparison. See next footnote.
M. Ibandronate vs. ~~zolendronate~~zoledronate (2 studies): RR = 0.52 (95% CI 0.19, 1.45). Clodro~~a~~nate vs. ~~zolendronate~~zoledronate (1 study): RR = 3.09 (95% CI 0.12, 77.2).

Trials

1. von Au, A., Milloth, E., Diel, I., et al. Intravenous pamidronate versus oral and intravenous clodronate in bone metastatic breast cancer: a randomized, open-label, non-inferiority Phase III trial. Onco Targets Ther; 2016.
2. Choudhury, K. B., Mallik, C., Sharma, S., Choudhury, D. B., Maiti, S., Roy, C. A randomized controlled trial to compare the efficacy of bisphosphonates in the management of painful bone metastasis. Indian J Palliat Care; Sep 2011.

3. Wang, F., Chen, W., Chen, H., et al. Comparison between zoledronic acid and clodronate in the treatment of prostate cancer patients with bone metastases. Med Oncol; 2013.
4. Barrett-Lee, P., Casbard, A., Abraham, J., et al. Oral ibandronic acid versus intravenous zoledronic acid in treatment of bone metastases from breast cancer: a randomised, open label, non-inferiority phase 3 trial. Lancet Oncol; Jan 2014.
5. Rosen, L. S., Gordon, D. H., Dugan, W.,Jr., et al. Zoledronic acid is superior to pamidronate for the treatment of bone metastases in breast carcinoma patients with at least one osteolytic lesion. Cancer; Jan 01 2004.
6. Francini, F., Pascucci, A., Bargagli, G., et al. Effects of intravenous zoledronic acid and oral ibandronate on early changes in markers of bone turnover in patients with bone metastases from non-small cell lung cancer. Int J Clin Oncol; Jun 2011.
7. Body, J. J., Lichinitser, M., Tjulandin, S., Garnero, P., Bergstrom, B. Oral ibandronate is as active as intravenous zoledronic acid for reducing bone turnover markers in women with breast cancer and bone metastases. Ann Oncol; Jul 2007.

Evidence-to-Decision table 5.2.2		
In adults (including older persons) and adolescents with bone metastases, what is the evidence for the use of bisphosphonates compared to other bisphosphonates in order to prevent and treat pain?		
POPULATION:	Adults (including older persons) and adolescents with cancer-related pain	**Background:** Bone pain is the most common type of pain from cancer and is present in approximately one out of three patients with bone metastases.[129,139]. The pain is commonly a mixture of background pain and incident/episodic pain, which is commonly associated with weight bearing or movement.[130] Bone metastases can weaken bone sufficiently to greatly increase patients' risk of fracture. Bisphosphonates inhibit osteoclasts, and their use in cancer patients prevents the elevated bone resorption common in metastatic bone disease. They thus reduce complications or skeletal related events (SREs), and reduce bone pain and analgesic requirements.[131,132] **Current WHO recommendation**: • The WHO 1996 cancer pain relief guidelines do not address the use of bisphosphonates. There are no GRC approved guidelines on the use of bisphosphonates for pain relief. • Zoledronic acid was added to the WHO Model list of essential medicines for adults in 2017. • 5.2.1 recommends that bisphosphonates be administered over placebo. This question is concerned about choice of bisphospho~~spho~~nate.
INTERVENTION:	Bisphosphonates	
COMPARISON:	Bisphosphonates	
MAIN OUTCOMES:	• Pain relief • Pain relief speed • Pain relief maintenance • Quality of life (QoL) • Functional outcomes • Skeletal-related events • Osteonecrosis of the jaw (adverse event)	
STRATIFICATIONS:	• Age (adults, older persons, adolescents, children) • History of substance abuse • Refractory pain	
SETTING:	All	
PERSPECTIVE:	Population	

	CRITERIA	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	**Research Evidence** None **Additional considerations** Bisphosphonates are commonly used in for pain relief in clinical practice. Yet WHO does not have guidance on their use.

BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Yes ☐ No ☐ Uncertain ☒ Yes	• **Seven randomized controlled trials** compared different bisphosphonates in patients with various cancers with bone metastases—mostly breast, prostate, and non-small cell lung cancer. The trials evaluated **clodronate, ibandronate, pamidronate, and zoledronate**. Trial participants were generally older, with mean ages ranging from 53 to 73 years old. **BENEFITS and HARMS** • **One trial** provided **low evidence** reported **no difference in average or worst pain between different bisphosphonates** (between group differences -2.6 [95% CI -11.8, 6.6] and -0.1 [95% CI -9.3, 9.1], respectively), and in percentage of people who achieve pain relief (by at least 50%) (RR = 1.38 [95% CI 0.55, 3.49]). • **No trial** reported on **pain relief speed**. • **Two trials** provided **very low strength of evidence regarding duration of pain relief.** One study found no difference in average duration of pain relief in patients with a variety of cancers (about half with lung cancer) between ibandronate (5.5 months) and pamidronate (5.2 months). One trial reported that in patients with prostate cancer those taking clodronate had longer duration of pain relief (13 months) than those taking zolendronate (9 months, P=0.03). • **No trial** reported on **QoL**. • **No trial** reported on **functional outcomes**. • **Six trials** provided **very low strength of evidence** that **skeletal-related events were similar across bisphosphonates** (18-26%, no data on pamidronate). • **Four trials** provided **very low strength of evidence** that **fracture rates were similar between bisphosphonates**, except in one trial of people with breast cancer in which 16% of those taking clodronate had fractures compared with 7% taking pamidronate (P=0.03). • **Three trials** provided **very low strength of evidence** of **no significant differences in rates of spinal cord compression across bisphosphonates**. • **Two trials** provided **very low strength of evidence** of **no significant differences in rates of bone radiotherapy across bisphosphonates**. • **Three trials** provided **very low strength of evidence** of **no significant differences in rates of bone surgery across bisphosphonates**. • **Three trials** provided **very low strength of evidence** of **rare rates of osteonecrosis of the jaw for clodronate (1.5%), ibandronate (0.7%), and zolendronate (1.2%)**; ibandronate vs. zolendronate (2 studies; RR = 0.52; 95% CI 0.19, 1.45); clodronate vs. zolendronate (1 study; RR = 3.09; 95% CI 0.12, 77.2). **STRATIFICATIONS** • Studies conducted in adults with a wide age range, without stratification into adolescent, non-older persons, and older persons. • Studies provide no data regarding history of substance abuse.

		• Studies provide no data regarading refractory pain. **SUMMARY** The choice of bisphosphonate may make little or no difference in bone pain relief. We are uncertain whether there are differences in effects of different bisphosphonates on other outcomes.

ACCEPTABILITY & PREFERENCES	**Is there important uncertainty or variability about how much people value the options?** Major variability [ ] Minor variability [Yes] Uncertain [ ] **Is the option acceptable to key stakeholders?** Yes No Uncertain [Yes] [ ] [ ]	**<u>Research evidence</u>** None **<u>Additional considerations</u>** The GDG did not think patients would have major reasons to prefer one bisphosphonate to another and thought there would only be minor variability. Clinicians might differ in their preferences for use of certain bisphosphonates, since there is evidence of differences in renal adverse effects and therefore the degree to which renal pathologies are considered to be contraindications.[140] This being the case, the options were all nevertheless considered acceptable to key stakeholders.

FEASIBILITY ./ RESOURCE USE

How large are the resource requirements?

Major	Minor	Uncertain
Yes		

Is the option feasible to implement?

Yes	No	Uncertain
		Yes

	Price (USD) per vial or tablet		
Medication	**International Medical Products Price Guide, Median price**	**Drugs.com**	**Pharmacychecker.com**
~~Zolendronate~~Zoledronate (4mg/5ml IV solution, 5ml)	$ 23.4501	$ 45.52	-
Clodronate (800mg)	NA	NA	$ 3.87
Ibandronate (3mg/3mL IV solution, 3ml)	NA	$ 218.56	-
Pamidronate (3mg/ml IV solution, 10ml)	NA	$ 20.16	-
Etidronate (200mg oral tablet)	NA	$ 3.17	-
Risendronate (35mg tablet)	NA	$ 38.75	-

- The GDG recognized the high costs of bisphosphonate medications.
- Most of the RCTs were conducted with intermittent intravenous administration. Using this method could be considered as a potential feasibility issue according to the GDG.

Would the option improve equity in health?

Yes	No	Uncertain
		Yes

Research Evidence

The use of bisphosphonates in populations of older women with osteoporosis and in breast cancer patients with bone metastases has been deemed cost-saving or cost effective (depending on population) in a number of high income countries.[133-135] It remains to be seen whether these savings would apply to lower income settings.

Additional considerations

Bisphosphonates are expensive throughout the world. In most settings, their use is often prohibitively expensive.

Combining these considerations, the GDG felt that equity could be affected in either direction, and therefore opted for uncertainty in this regard.

Recommendation	**Current recommendation:** None **New (draft) recommendation:** None
Strength of Recommendation	None
Quality of Evidence	➢ **VERY LOW** [Pain (critical) = low Pain reduction maintenance (critical) = very low Skeletal-related events (important) = very low (any, fracture, spinal cord compression, bone radiation therapy, bone surgery, hypercalcemia) Osteonecrosis of jaw (important) = low other outcomes omitted for no data]
Justification	The GDG did not feel the evidence permitted recommending one bisphosphonate over another.
Subgroup considerations	
Implementation considerations [incl. M&E]	
Research priorities	

5.2.3. Monoclonals vs. Placebo

A single eligible study compared monoclonals to placebo (Evidence Profile 5.2.3). The study evaluated tanezumab in adults with prostate cancer, breast cancer, renal cell carcinoma, or multiple myeloma with painful bone metastases (mean age 56 years, range 32 to 77).[141]

The study provided very low strength of evidence of no difference in average or worst pain between groups (between group differences -2.6 [95% CI -11.8, 6.6] and -0.1 [95% CI -9.3, 9.1], respectively), and in percentage of people who achieve pain relief (by at least 50%) (RR = 1.38 [95% CI 0.55, 3.49]).

The study did not report on speed of pain relief, duration of pain relief maintenance, quality of life, or functional outcomes.

The study provided very low strength of evidence regarding skeletal-related events, reporting only that 1 of 29 (3.4%) patients in the tanezumab arm had a femur fracture but, implicitly, none of the 30 people on placebo had a fracture (although one had undefined metastatic disease progression).

No study reported on osteonecrosis of the jaw.

Evidence Profile 5.2.3. Monoclonals vs. Placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Monoclonal	Placebo	Relative (95% CI)	Absolute (95% CI)		
Pain relief (categorical) (follow up:8 week)												
1 [1]	RCT	not serious	N/A	not serious	serious	single study	8/29 (28%)	6/30 (20%)	**RR 1.38** (0.55, 3.49)	**76 more per 1000** (from 91 fewer to 497 more)	Very Low	CRITICAL
Pain relief (continuous) (follow up:8 weeks; assessed with: VAS; Scale: 0 to 100 [worst]*)												
1 [1]	RCT	not serious	N/A	not serious	serious	single study	29	30	**Average pain: Diff -2.6** (-11.8, 6.6) **Worst pain: Diff -0.1** (-9.3, 9.1)		Very Low	CRITICAL
Pain relief speed												
0									not estimable	-	-	IMPORANT
Pain reduction maintenance												
0									not estimable	-	-	CRITICAL
Skeletal related events, fracture (follow up:8 weeks)												
1 [1]	RCT	not serious	N/A	not serious	very serious [B]	single study	1/29 (3.4%)	0/30 (0%)	**RR 3.10** (0.13, 73.2)		Very Low	IMPORTANT
Quality of life												
0									not estimable	-	-	CRITICAL
Functional outcomes												
0									not estimable	-	-	CRITICAL
Adverse events: Osteonecrosis of the jaw												
0									not estimable			IMPORTANT

Abbreviations: CI: *confidence interval;* ***Diff:*** *difference (between groups);* ***N/A****: not applicable,* ***NS****: not statistically significant;* ***RCT:*** *randomized controlled trial(s);* ***RR****: relative risk (log scale).*

Explanations

A. All comparisons were statistically nonsignificant. “Any serious adverse” event occurred in 7/29 (24%) vs. 4/30 (13%) (tanezumab vs. placebo), nausea 17% vs. 7%, vomiting 7% both, arthralgia 0% vs. 3%, and constipation 10% vs. 7%.

B. Small sample size, rare events, and very wide confidence interval,

Trials

1. Sopata, M., Katz, N., Carey, W., Smith, M. D., Keller, D., Verburg, K. M., West, C. R., Wolfram, G., Brown, M. T.. Efficacy and safety of tanezumab in the treatment of pain from bone metastases. Pain; Sep 2015.

Evidence-to-Decision table 5.2.3		
In adults (including older persons) and adolescents with bone metastases, what is the evidence for the use of monoclonal antibodies (monoclonals) compared to no treatment in order to prevent and treat pain?		
POPULATION:	Adults (including older persons) and adolescents with cancer-related pain	**Background:** Bone pain is the most common type of pain from cancer and is present in approximately one out of three patients with bone metastases.[129,139] The pain is commonly a mixture of background pain and incident/episodic pain, which is commonly associated with weight bearing or movement.[130] Bone metastases can weaken bone sufficiently to greatly increase patients' risk of fracture. There are reports that monoclonal antibodies designed to target Nerve Growth Factor (NGF) and osteoclasts reduce pain scores in patients with metastatic bone pain[141] or fracture risk[142]. **Current WHO recommendation**: None.
INTERVENTION:	Monoclonals	
COMPARISON:	Placebo (no treatment)	
MAIN OUTCOMES:	• Pain relief • Pain relief speed • Pain relief maintenance • Quality of life (QoL) • Functional outcomes • Skeletal-related events • Osteonecrosis of the jaw (adverse event)	
STRATIFICATIONS:	• Age (adults, older persons, adolescents, children) • History of substance abuse • Refractory pain	
SETTING:	All	
PERSPECTIVE:	Population	

	CRITERIA	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** Yes	**Research evidence** None **Additional considerations** WHO does not have recommendations for treating bone pain and should investigate the various methods by which it might be treated, monoclonal antibodies being one of these methods.

BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Yes: ☐ No: ☐ Uncertain: ☒ Yes	• **One randomized controlled trial** compared monoclonals to placebo, evaluating **tanezumab** in adults with prostate cancer, breast cancer, renal cell carcinoma, or multiple myeloma with painful bone metastases (mean age 56 years, range 32 to 77). **BENEFITS and HARMS** • **One trial** provided **very low strength of evidence** reported **no difference in average or worst pain between tanezumab and placebo** (between group differences -2.6 [95% CI -11.8, 6.6] and -0.1 [95% CI -9.3, 9.1], respectively), and in percentage of people who achieve pain relief (by at least 50%) (RR = 1.38 [95% CI 0.55, 3.49]). • **No trial** reported on **pain relief speed**. • **No trial** reported on **pain relief maintenance**. • **No trial** reported on **QoL**. • **No trial** reported on **functional outcomes**. • **One trial** provided **very low strength of evidence** of **increased skeletal-related events with monoclonals**, reporting only that 1 of 29 (3.4%) patients in the tanezumab arm had a femur **fracture** (RR = 3.1 [95% CI 0.13, 73.2]). • **No trial** reported on **osteonecrosis of the jaw**. **STRATIFICATIONS** • Studies conducted in adults with a wide age range, without stratification into adolescent, non-older persons, and older persons. • Studies provide no data regarding history of substance abuse. • Studies provide no data regarading refractory pain. **SUMMARY** We are uncertain whether monoclonals affect outcomes compared to placebo.

ACCEPTABILITY & PREFERENCES	**Is there important uncertainty or variability about how much people value the options?** Major variability [ ] Minor variability [ ] Uncertain [Yes] **Is the option acceptable to key stakeholders?** Yes [ ] No [ ] Uncertain [Yes]	**<u>Research evidence</u>** None **<u>Additional considerations</u>** None

FEASIBILITY ./ RESOURCE USE	**How large are the resource requirements?** Major Minor Uncertai [ ] [ ] [Yes] **Is the option feasible to implement?** Yes No Uncertain [ ] [ ] [Yes]	**Research evidence** The price of Tanezumab could not be found. **Additional considerations** None
	Would the option improve equity in health? Yes No Uncertai [ ] [ ] [Yes]	**Research evidence** None **Additional considerations** None

Recommendation	**Current recommendation:** None **New (draft) recommendation:** None
Strength of Recommendation	
Quality of Evidence	➢ **VERY LOW** [Pain (critical) = very low others omitted for no data or indeterminate findings]
Justification	The GDG did not feel it could make a recommendation on the basis of the eligible evidence. They noted that the paucity of trials probably derives from the preference to trial new therapies against the usual treatment rather than placebo.
Subgroup considerations	
Implementation considerations [incl. M&E]	
Research priorities	

5.2.4. Comparisons of Monoclonals

No eligible studies were found that address this sub-question.

Evidence-to-Decision table 5.2.4		
In adults (including older persons) and adolescents with bone metastases, what is the evidence for the use of monoclonal antibodies (monoclonals) compared to each other in order to prevent and treat pain?		
POPULATION:	Adults (including older persons) and adolescents with cancer-related pain	**Background:** Bone pain is the most common type of pain from cancer and is present in approximately one out of three patients with bone metastases.[129,139] The pain is commonly a mixture of background pain and incident/episodic pain, which is commonly associated with weight bearing or movement.[130] Bone metastases can weaken bone sufficiently to greatly increase patients' risk of fracture. There are reports that monoclonal antibodies designed to target Nerve Growth Factor (NGF) and osteoclasts reduce pain scores in patients with metastatic bone pain[141] or fracture risk[142]. **Current WHO recommendation**: None
INTERVENTION:	Monoclonals	
COMPARISON:	Monoclonals	
MAIN OUTCOMES:	• Pain relief • Pain relief speed • Pain relief maintenance • Quality of life (QoL) • Functional outcomes • Skeletal-related events • Osteonecrosis of the jaw (adverse event)	
STRATIFICATIONS:	• Age (adults, older persons, adolescents, children) • History of substance abuse • Refractory pain	
SETTING:	All	
PERSPECTIVE:	Population	

	CRITERIA	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** Yes	**Research evidence** None **Additional considerations** WHO does not have recommendations for treating bone pain and should investigate the various methods by which it might be treated, monoclonal antibodies being one of these methods.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Yes ☐ No ☐ Uncertain ☐ Yes	• **No randomized controlled trial** compared monoclonal antibodies. **BENEFITS and HARMS** • **No trial** reported on **pain relief**. • **No trial** reported on **pain relief speed**. • **No trial** reported on **pain relief maintenance**. • **No trial** reported on **QoL**. • **No trial** reported on **functional outcomes**. • **No trial** reported on **skeletal-related events**. • **No trial** reported on **osteonecrosis of the jaw**. **STRATIFICATIONS** • Studies conducted in adults with a wide age range, without stratification into adolescent, non-older persons, and older persons. • Studies provide no data regarding history of substance abuse. • Studies provide no data regarading refractory pain. **SUMMARY** No eligible trials were found that address this sub-question.

ACCEPTABILITY & PREFERENCES	**Is there important uncertainty or variability about how much people value the options?** Major variability [ ] Minor variability [ ] Uncertain [Yes] **Is the option acceptable to key stakeholders?** Yes [ ] No [ ] Uncertain [Yes]	**<u>Research evidence</u>** None **<u>Additional considerations</u>** None

FEASIBILITY ./ RESOURCE USE	**How large are the resource requirements?** Major Minor Uncertai Yes **Is the option feasible to implement?** Yes No Uncertair Yes	**Research evidence** None **Additional considerations** None
EQUITY	**Would the option improve equity in health?** Yes No Uncertai Yes	**Research evidence** None **Additional considerations** None

Recommendation	**Current recommendation:** None **New (draft) recommendation:** None
Strength of Recommendation	
Quality of Evidence	➢ None [Omitted for no data]
Justification	
Subgroup considerations	
Implementation considerations [incl. M&E]	
Research priorities	

5.2.5. Monoclonals vs. Bisphosphonates

Nine eligible trials compared monoclonal antibodies and bisphosphonates (Evidence Profile 5.2.5).[142-150] All evaluated the monoclonal denosumab; most evaluated ~~zolendronate~~zoledronate, but also pamidronate, or a variety of bisphosphonates (based on local practice). Studies included patients with metastatic bone lesions, mostly from breast or prostate cancer, but also non-small cell lung cancer, multiple myeloma, and other cancers. Three trials with identical protocols,[146-148] except for which cancers were eligible, were separately conducted and reported, but also combined and reported in a summary article.[142] Patient ages varied widely across studies.

One study provided low strength of evidence for pain relief and time until pain relief (speed) and very low strength of evidence for quality of life.[150] The study included people with either breast cancer or multiple myeloma and compared denosumab and ~~zolendronate~~zoledronate. The study found no difference in the percentage of people who had decreases in their pain scores of at least 2 (of 10) points (RR = 0.89; 95% CI 0.67, 1.10); they did not evaluate complete pain relief. The study also found no difference in average time until this pain outcome was reached (2.7 vs. 2.6 months). The study also found no significant difference in quality of life, as assessed by an improvement of at least 5 (of 108) points in FACT-G (Functional Assessment of Cancer Therapy–General; RR = 1.08; 95% CI 0.95, 1.23). No study evaluated pain reduction maintenance.

The studies provide (mostly) high strength of evidence favoring denosumab over bisphosphonates to prevent skeletal-related events. Across six studies, rates of any skeletal-related event (summary RR = 0.86; 95% CI 0.81, 0.91), fracture (summary RR = 0.88; 95% CI 0.78, 0.96), bone radiation therapy (summary RR = 0.80; 95% CI 0.73, 0.88), and hypercalcemia (summary RR = 0.58; 95% CI 0.34, 0.81) were statistically significantly more common among those treated with bisphosphonates. Spinal cord compression and bone surgery were rarer events, but also occurred less frequently among patients taking denosumab, although the differences were nonsignificant in a single study reporting spinal cord compression (RR = 0.88; 95% CI 0.65, 1.20) and bone surgery (RR = 0.87; 95% CI 0.62 to 1.23). Because only a single study reported these outcomes, they were deemed to have moderate strength of evidence.

Two studies provided low strength of evidence for functional outcomes. The studies both reported that people taking denosumab had better functional outcomes than those on ~~zolendronate~~zoledronate, although in both studies the differences were not statistically significant. The studies evaluated time to increase (worsening) in interference due to pain (16 vs 14.9 months) and ECOG performance status (RR = 1.07 [95% CI 0.99, 1.16]). Three studies provide high strength of evidence regarding the risk of osteonecrosis of the jaw. The adverse event was more common with denosumab than bisphosph~~p~~onates, with a summary RR = 1.40 (95% CI 0.92, 2.13).

Evidence Profile 5.2.5. Monoclonals vs. Bisphosphonates

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Monoclonal (Denosumab)	Bisphosphonate	Relative (95% CI)	Absolute (95% CI)		
Pain relief (categorical) (follow up: 18 months)												
1 [1]	RCT	serious [A]	not serious	serious [B]	not serious	single study	156/975 (16%) [B]	171/951 (18%) [B]	**RR 0.89** [B] (0.67 to 1.10)	**20 fewer per 1,000** (from 15 more to 49 fewer)	Low	CRITICAL
Pain relief speed (follow up: 18 months)												
1 [1]	RCT	serious [A]	not serious	not serious	not serious	single study	747	745	**HR 1.02** (0.91, 1.15) [2.7 vs. 2.6 months]	**0.1 month**	Low	IMPORTANT
Pain reduction maintenance												
0									not estimable			CRITICAL
Skeletal-related events, any (follow up: range 25 weeks to 41 months)												
6 [2,3,4,5,6,7,8, C]	RCT	not serious	not serious	not serious	not serious	none	1284/4172 (31%)	1461/3959 (37%)	**RR 0.86** (0.81 to 0.91)	**39 fewer per 1000** (from 24 to 53 fewer)	High	IMPORTANT
Skeletal-related events, fracture (follow up: 18 months)												
2 [3, 5]	RCT	not serious	not serious	not serious	not serious	none	743/3888 (19%)	840/3881 (22%)	**RR 0.88** (0.78 to 0.96)	**26 fewer per 1000** (from 8 to 42 fewer)	High	IMPORTANT
Skeletal-related events, spinal cord compression (follow up: nd)												
1 [5]	RCT	not serious	not serious	not serious	not serious	single study	76/2862 (2.7%)	86/2861 (3.0%)	**RR 0.88** (0.65 to 1.20)	**4 fewer per 1000** (from 6 more to 10 fewer)	Moderate	IMPORTANT
Skeletal-related events, bone radiation (follow up: 18 months)												
2 [3, 5]	RCT	not serious	not serious	not serious	not serious	none	632/3888 (16%)	787/3881 (20%)	**RR 0.80** (0.73 to 0.88)	**37 fewer per 1000** (from 22 to 51 fewer)	High	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Monoclonal (Denosumab)	Bisphosphonate	Relative (95% CI)	Absolute (95% CI)		
Skeletal-related events, bone surgery (follow up: nd)												
1 [5]	RCT	not serious	not serious	not serious	not serious	single study	64/2862 (2.2%)	72/2861 (2.5%)	**RR 0.87** (0.62 to 1.23)	**3 fewer per 1000** (from 6 more to 9 fewer)	Moderate	IMPORTANT
Skeletal-related events, hypercalcemia (follow up: 18 months)												
2 [3, 5]	RCT	not serious	not serious	not serious	not serious	none	64/3888 (1.6%)	111/3881 (2.9%)	**RR 0.58** (0.34 to 0.81)	**16 fewer per 1000** (from 7 to 22 fewer)	High	IMPORTANT
Quality of life (follow up: 18 months; assessed with: FACT-G; Scale: 0 to 100 [best] [D])												
1 [1]	RCT	serious [A]	not serious	serious [E]	not serious	single study	314/956 (33%) [F]	290/952 (30%) [F]	**RR 1.08** (0.95 to 1.23) [F]	**24 more per 1000** (from 17 fewer to 70 more)	Very Low	CRITICAL
Functional outcomes (follow up: 18 months; assessed with: ECOG; Scale: 0 to 100 [best] [D])												
2 [1,3]	RCT	serious [A]	not serious	serious [E]	not serious	none	1703	1697	**HR 0.89** (0.78 to 1.02) [16.0 vs. 14.9 mo] [G] **RR 1.07** (0.99 to 1.16) [H]	**1.1 month** **41 more per 1000** (from 4 fewer to 89 more)	Low	IMPORTANT
Adverse events: Osteonecrosis of the jaw (follow up: range 2.8 month to 41 months)												
3 [5 C]	RCT	not serious	not serious	not serious	not serious	none	52/2841 (1.8%)	37/2836 (1.3%)	**RR 1.40** (0.92, 2.13)	**5 more per 1000** (from 1 fewer to12 more)	High	IMPORTANT

Abbreviations: CI: *confidence interval;* ***ECOG:*** *Eastern Cooperative Oncology Group scale;* ***FACT-G****: Functional Assessment of Cancer Therapy–General****; HR:*** *hazard ratio;* ***N/A:*** *not applicable;* ***nd****: no data;* ***NS:*** *not statistically significant;* ***OR****: odds ratio;* ***RCT:*** *randomized controlled trial(s);* ***RR****: relative risk (log scale);* ***SRE:*** *skeletal-related event(s).*

Explanations

A. High percentage not analyzed.
B. Outcome is a decrease in pain by >=2/10 points, not pain relief.
C. Some data were compiled from Lipton 2012 (PMID 22975218), which combined Fizazi 2011 (PMID 21353695), Henry 2011 (PMID 21343556), and Stopeck 2010 (PMID 21060033).
D. Scales transformed to 0 to 100, as necessary.
E. FACT (total score) is a measure of quality of life that mix concepts of both quality of life and functional outcomes.
F. Improvement in FACT-G >=5/108 points.

G. Time to increase (worsening) in interference due to pain >=2/10 points, favors monoclonal.
H. ECOG performance status maintained, favors monoclonal.

Trials

1. Cleeland, C. S., Body, J. J., Stopeck, A., et al. Pain outcomes in patients with advanced breast cancer and bone metastases: results from a randomized, double-blind study of denosumab and zoledronic acid. Cancer; Feb 15 2013.
2. Stopeck, A. T., Lipton, A., Body, J. J., et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. J Clin Oncol; Dec 10 2010.
3. Martin, M., Bell, R., Bourgeois, H., et al. Bone-related complications and quality of life in advanced breast cancer: results from a randomized phase III trial of denosumab versus zoledronic acid. Clin Cancer Res; Sep 01 2012.
4. Lipton, A., Steger, G. G., Figueroa, J., et al. Extended efficacy and safety of denosumab in breast cancer patients with bone metastases not receiving prior bisphosphonate therapy. Clin Cancer Res; Oct 15 2008.
5. Lipton, A., Fizazi, K., Stopeck, A. T., et al. Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: a combined analysis of 3 pivotal, randomised, phase 3 trials. Eur J Cancer; Nov 2012.
6. Henry, D. H., Costa, L., Goldwasser, F., et al. Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. J Clin Oncol; Mar 20 2011.
7. Fizazi, K., Carducci, M., Smith, M., et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. Lancet; Mar 05 2011.
8. Fizazi, K., Lipton, A., Mariette, X., et al. Randomized phase II trial of denosumab in patients with bone metastases from prostate cancer, breast cancer, or other neoplasms after intravenous bisphosphonates. J Clin Oncol; Apr 01 2009.
9. Body, J. J., Facon, T., Coleman, R. E., et al. A study of the biological receptor activator of nuclear factor-kappaB ligand inhibitor, denosumab, in patients with multiple myeloma or bone metastases from breast cancer. Clin Cancer Res; Feb 15 2006.

Evidence-to-Decision table 5.2.5		
In adults (including older persons) and adolescents with bone metastases, what is the evidence for the use of monoclonal antibodies (monoclonals) compared to bisphosphonates to prevent and treat pain?		
POPULATION:	Adults (including older persons) and adolescents with cancer-related pain	**Background:** Bone pain is the most common type of pain from cancer and is present in approximately one out of three patients with bone metastases.[129,139] The pain is commonly a mixture of background pain and incident/episodic pain, which is commonly associated with weight bearing or movement.[130] Bone metastases can weaken bone sufficiently to greatly increase patients' risk of fracture. Bisphosphonates and monoclonal antibodies are two classes of medication reported to relieve bone pain in cancer patients. Bisphosphonates inhibit osteoclasts, and their use in cancer patients prevents the elevated bone resorption common in metastatic bone disease. They thus reduce complications or skeletal related events (SREs), and reduce bone pain and analgesic requirements.[131] There are reports that monoclonal antibodies designed to target Nerve Growth Factor (NGF) and osteoclasts reduce pain scores in patients with metastatic bone pain[141] or fracture risk[142]. **Current WHO recommendation**: None
INTERVENTION:	Monoclonals	
COMPARISON:	Bisphosphonates	
MAIN OUTCOMES:	• Pain relief • Pain relief speed • Pain relief maintenance • Quality of life (QoL) • Functional outcomes • Skeletal-related events • Osteonecrosis of the jaw (adverse event)	
STRATIFICATIONS:	• Age (adults, older persons, adolescents, children) • History of substance abuse • Refractory pain	
SETTING:	All	
PERSPECTIVE:	Population	

	CRITERIA	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** Yes	**Research evidence** None **Additional considerations** WHO does not have recommendations for treating bone pain and should investigate the various methods by which it might be treated, including both bisphosphonates and monoclonal antibodies.

BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Yes No Uncertain Yes	• **No randomized controlled trials** compared monoclonals to bisphosphonates in patients with metastatic bone lesions, mostly from breast or prostate cancer, but also non-small cell lung cancer, multiple myeloma, and other cancers; although most studies did not report the cancer types. All evaluated the monoclonal denosumab; most evaluated zolendronate, but also pamidronate, or a variety of bisphosphonates (based on local practice). Patient ages varied widely across trials. **BENEFITS and HARMS** • **One trial** provided **low strength of evidence** that **there was no difference between monoclonals** (denosumab) **and bisphosphonates** (zolendronate) **in the percentage of people who had decreases in their pain scores** of at least 2 (of 10) points **(**RR = 0.89; 95% CI 0.67, 1.10); the trial did not evaluate complete pain relief. • **One trial** provided **low strength of evidence**that found **no difference between monoclonals** (denosumab) **and bisphosphonates** (zolendronate) **in average time until this pain outcome was reached** (2.7 vs. 2.6 months). • **No trial** reported on **pain relief maintenance**. • **Six trials** provide **high strength of evidence favoring monoclonals over bisphosphonates to prevent any skeletal-related events** (summary RR = 0.86; 95% CI 0.81, 0.91). • **Two trials** provided **high strength of evidence favoring monoclonals over bisphosphonates to prevent fractures** (summary RR = 0.88; 95% CI 0.78, 0.96). • **One trial** provided **moderate strength of evidence favoring monoclonals over bisphosphonates to prevent spinal cord compression** (summary RR = 0.88; 95% CI 0.65, 1.20). • **Two trials** provided **high strength of evidence favoring monoclonals over bisphosphonates to prevent bone radiation therapy** (summary RR = 0.80; 95% CI 0.73, 0.88). • **One trial** provided **moderate strength of evidence favoring monoclonals over bisphosphonates to prevent bone surgery** (summary RR = 0.87; 95% CI 0.62, 1.23). • **Two trials** provided **high strength of evidence favoring monoclonals over bisphosphonates to prevent hypercalcemia** (summary RR = 0.58; 95% CI 0.34, 0.81). • **One trial** provided **very low strength of evidence** regarding **QoL**. As assessed by an improvement of at least 5 (of 108) points in FACT-G (Functional Assessment of Cancer Therapy–General, RR = 1.08; 95% CI 0.95, 1.23). We are uncertain of any difference. • **Two trials** provided **low strength of evidence** regarding **functional outcomes**, **favoring monoclonals** (denosumab) **over bisphosphonates** (zolendronate): time to increase (worsening) in interference due to pain (16 vs 14.9 months) and ECOG performance status (RR = 1.07 [95% CI 0.99, 1.16]). • **Three trials** provide **high strength of evidence** that **the risk of osteonecrosis of the jaw was more common with monoclonals than bisphosphponates**, with a summary RR = 1.40 (95% CI 0.92, 2.13). **STRATIFICATIONS**

		• Studies conducted in adults with a wide age range, without stratification into adolescent, non-older persons, and older persons. • Studies provide no data regarding history of substance abuse. • Studies provide no data regarading refractory pain. **SUMMARY** Monoclonals reduce the risk of skeletal-related events and may improve functional outcomes more than bisphosphonates, but increase the risk of osteonecrosis of the jaw. The choice of monoclonals or bisphosphonates may make little or no difference to bone pain, or time to pain relief.

ACCEPTABILITY & PREFERENCES	**Is there important uncertainty or variability about how much people value the options?** Major variability Yes Minor variability Uncertain **Is the option acceptable to key stakeholders?** Yes No Uncertain Yes	**Research evidence** None **Additional considerations** Monoclonal antibody regimens involve a lower medication-administration burden than bisphosphonates, which patients would prefer. But they also have a higher cost, which patients would not ~~dis~~prefer. Osteonecrosis of necrosis of the jaw (higher with monoclonal antibodies) is an outcome sufficiently adverse that the GDG believe it could affect patient preferences, but its expected disutility to patients must be weighed against the expected disutility of skeletal-related events (higher with bisphosphonates). The therapies were both deemed acceptable to clinicians and other key stakeholders.

FEASIBILITY ./ RESOURCE USE

How large are the resource requirements?

Major	Minor	Uncertai
Yes		

Is the option feasible to implement?

Yes	No	Uncertain
Yes		

Medication	Price (USD) per vial or tablet				
	International Medical Products Price Guide, Median price*	Drugs.com*	Pharmacychecker.com*	Goodrx.com*	Green et al. 2010 [151]
Zoledronate (4mg/5ml IV solution, 5ml)	$ 23.4501	$ 45.52	-	-	-
Clodronate (800mg)	Not present	NA	$ 3.87	-	-
Ibandronate (3mg/3mL IV solution, 3ml)	Not present	$ 218.56	-	-	-
Pamidronate (3mg/ml IV solution, 10ml)	Not present	$ 20.16	-	-	-
Etidronate (200mg oral tablet)	Not present	$ 3.17	-	-	-
Risendronate (35mg tablet)	Not present	$ 38.75	-	-	-
Denosumab (60mg/ml, 1ml syringe)	Not present	Not present	$ 553.68	$1121.15	$990.00

*All accessed 16th January 2018. Prices reported here are the lowest prices reported at the sources.

Would the option improve equity in health?

Yes	No	Uncertai
	Yes	

Research evidence

None

Additional considerations

There is a major equity issue with the recommendation of denosumab.

Recommendation	**Current recommendation:** None **New (draft) recommendation:** None
Strength of Recommendation	**None**
Quality of Evidence	➢ **MODERATE/LOW** [Pain (critical) = low Skeletal related events (important) = high (any, fracture, bone radiation therapy, hypercalcemia), moderate (spinal cord compression, bone surgery) Functional outcomes (important) = moderate Osteonecrosis of the jaw (important) = high]
Justification	Monoclonals reduce the risk of skeletal-related events and may improve functional outcomes more than bisphosphonates, but increase the risk of osteonecrosis of the jaw. The choice of monoclonals or bisphosphonates may make little or no difference to bone pain, or time to pain relief. Although there are relative benefits to the use of denosumab compared with bisphosphonates, the relative cost of denosumab is disproportionate to the benefits. The GDG felt that they could not recommend one medication over the other on these grounds.
Subgroup considerations	
Implementation considerations [incl. M&E]	
Research priorities	

5.3. In adults (including older persons) and adolescents with cancer-related neuropathic pain, what is the evidence for the use of anti-depressants compared with placebo, no anti-depressant or other anti-depressants in order to relieve pain?

The systematic review team have divided Key Question 5.3 into two sections: anti-depressants versus placebo (or no anti-depressant) and comparison of anti-depressants.

5.3.1 Anti-depressants vs. Placebo (or No Anti-Depressant)

One eligible study compared anti-depressants to placebo (see Evidence Profile 5.3). The study evaluated amitriptyline in people with severe neuropathic cancer pain (cancer types not reported). The study did not report participant ages. The RCT findings are summarized in Evidence Profile 5.3. The study provided evidence only regarding change in pain scores. It provided low strength of evidence that amitriptyline is more effective than placebo to reduce pain in people with cancer-related neuropathic pain; the net difference in VAS score (transformed 0 to 100 [worst] scale) was -4.7 (95% CI -9.2, -0.2). The trial did not report data on complete pain relief, pain relief speed, pain reduction maintenance, quality of life, functional outcomes, or adverse events.

Evidence Profile 5.3. Anti-Depressants vs. Placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Anti-depressants**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Pain relief (categorical) (follow up: range 4 weeks to 5 weeks; assessed with: BPI, Scale: 0 to 100 [worst] [A])												
0									not estimable			CRITICAL
Pain relief (continuous) (follow up: range 4 weeks to 5 weeks; assessed with: BPI, VAS; Scale: 0 to 100 [worst] [A])												
1 [1]	RCT	not serious	N/A	not serious	serious [B]	single study	30	30	**Net Diff -4.7** (-9.2, -0.2)		Low	CRITICAL
Pain relief speed												
0									not estimable			IMPORTANT
Pain reduction maintenance												
0									not estimable			CRITICAL
Quality of life												
0									not estimable			IMPORTANT
Functional outcomes												
0									not estimable			IMPORTANT
Adverse events: Sedation (somnolence, follow-up 5 weeks)												
0									not estimable			IMPORTANT
Adverse events: Anxiety or tremor												
0									not estimable			IMPORTANT

Abbreviations: *BPI**: Brief Pain Inventory; CI:** Confidence interval; **Diff:** difference (between groups); **RR:** relative risk (log scale); **RCT**: randomized controlled trial(s); **VAS**: Visual Analog Scale.*

Explanations

A. Scales transformed to 0 to 100, as necessary.
B. Small study.

Trials

1. Mishra, S., Bhatnagar, S., Goyal, G. N., Rana, S. P., Upadhya, S. P. A comparative efficacy of amitriptyline, gabapentin, and pregabalin in neuropathic cancer pain: a prospective randomized double-blind placebo-controlled study. Am J Hosp Palliat Care; May 2012.

Evidence-to-Decision table 5.3.1		
In adults (including older persons) and adolescents with cancer-related neuropathic pain, what is the evidence for the use of anti-depressants compared to placebo in order to relieve pain?		
POPULATION:	Adults (including older persons) and adolescents with cancer-related pain	**Background:** • Cancer-related neuropathic pain is common. It can be caused by the disease or due to acute or chronic effects of cancer treatment. Anti-depressants used in neuropathic pain treatment include tricyclic antidepressants (TCAs) and selective serotonin norepinephrine reuptake inhibitors (SNRIs). Some evidence exists to suggests their efficacy in neuropathic pain.[152] **Current WHO recommendation**: • As with nociceptive pain, pharmacotherapy is the mainstay of management for neuropathic pain. One or more of the following groups of medications may help: ○ Tricyclic antidepressants ○ Anticonvulsants ○ Local anesthetic congeners (class I antiarrhythmics) • Patients with neuropathic pain may derive benefit from opioids, particularly in cases of nerve compression. However, nerve compression pain may respond only if a corticosteroid is added. Mixed nociceptive and neuropathic pain will also benefit from morphine. Superficial burning pain and spontaneous stabbing pain associated with nerve injury often responds best to a tricyclic antidepressant or an anticonvulsant. • With regard to tricyclic antidepressants- Amitriptyline and imipramine are both widely available. Alternative preparations are available in many countries and may be more suitable for some patients. Nortriptyline does not have a sedative effect; desipramine is relatively nonsedative and has minimal anticholinergic. The starting dose will depend on the patient's age, weight, previous use of such medications and concurrent medication. A dose as low as 10mg may be appropriate for some patients, but most can take 25-50mg. The dose should be increased to 30-50mg as rapidly as can be tolerated in terms of sedation, postural hypotension and dry mouth. After that, increments should be made on a weekly basis until the pain is relieved or adverse effects preclude further escalation. Except with nortriptyline, the total daily dose should be given at bedtime, because most tricyclic antidepressants have a sedative effect. An
INTERVENTION:	Anti-depressants	
COMPARISON:	Placebo (no treatment)	
MAIN OUTCOMES:	• Pain relief • Pain relief speed • Pain relief maintenance • Quality of life (QoL) • Functional outcomes • Sedation (adverse event) • Anxiety or tremor (adverse event)	
STRATIFICATIONS:	• Age (adults, older persons, adolescents, children) • History of substance abuse • Refractory pain	
SETTING:	All	
PERSPECTIVE:	Population	

		analgesic effect is seen in many patients after a few days on doses of 50-100mg. The pain is always completely relieved.

	CRITERIA	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** Yes	**Research evidence** Cancer-related neuropathic pain is common. It can be caused by the disease or due to acute or chronic effects of cancer treatment. Anti-depressants used in neuropathic pain treatment include tricyclic antidepressants (TCAs) and selective serotonin norepinephrine reuptake inhibitors (SNRIs). Some evidence exists to suggests their efficacy in neuropathic pain[152]. WHO should issue updated guidance on their use. **Additional considerations** None

BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Yes No Uncertain Yes	• **One randomized controlled trial** compared an anti-depressant to placebo. The trial evaluated amitriptyline in people with severe neuropathic cancer pain (cancer types not reported). The trial did not report participant ages. **BENEFITS and HARMS** • **One trial** provided **low strength of evidence** that **anti-depressants (amitriptyline) are more effective than placebo to reduce pain** (difference between groups -4.7 [95% CI -9.2, -0.2] on a transformed 0 to 100 [worst] scale). • **No trial** reported on **pain relief speed**. • **No trial** reported on **pain relief maintenance**. • **No trial** reported on **QoL**. • **No trial** reported on **functional outcomes**. • **No trial** reported on **somnolence** as an adverse event. • **No trial** reported on **anxiety or tremor**. **STRATIFICATIONS** • Studies conducted in adults with a wide age range, without stratification into adolescent, non-older persons, and older persons. • Studies provide no data regarding history of substance abuse. • Studies provide no data regarading refractory pain. **SUMMARY** Anti-depressants probably provide greater pain relief than placebo.

ACCEPTABILITY & PREFERENCES	**Is there important uncertainty or variability about how much people value the options?** Major variability [ ] Minor variability [Yes] Uncertain [ ] **Is the option acceptable to key stakeholders?** Yes No Uncertain [Yes] [ ] [ ]	**<u>Research evidence</u>** None **<u>Additional considerations</u>** The GDG believed that some patients could have strong aversions to the use of antidepressants.

FEASIBILITY ./ RESOURCE USE	**How large are the resource requirements?** Major ☐ Minor ☐ Uncertai Yes **Is the option feasible to implement?** Yes ☐ No ☐ Uncertain Yes	**Research evidence** None **Additional considerations** None
	Would the option improve equity in health? Yes ☐ No ☐ Uncertai Yes	**Research evidence** None **Additional considerations** None

Recommendation	**Current recommendation:** None. **New (draft) recommendation:** None.
Strength of Recommendation	
Quality of Evidence	➢ **LOW** [Pain (critical) = low others omitted for no data]
Justification	While the GDG agreed that antidepressants have been found in decades of clinical practice to be effective in neuropathic pain syndromes, they cannot say that evidence suggests their effectiveness in tumour-related neuropathy. They therefore opted to make no recommendation due to lack of evidence.
Subgroup considerations	
Implementation considerations [incl. M&E]	
Research priorities	RCTs that assess the intervention in this population of patients, measured by comparable outcomes, are required to justify the indication of anti-depressants for cancer-related neuropathic pain.

5.3.2. Comparisons of Anti-Depressants

No eligible studies were found that address this sub-question.

<table>
<tr><th colspan="3">Evidence-to-Decision table 5.3.2</th></tr>
<tr><td colspan="3">In adults (including older persons) and adolescents with cancer-related neuropathic pain, what is the evidence for the use of anti-depressants compared to other anti-depressants in order to relieve pain?</td></tr>
<tr><td>POPULATION:</td><td>Adults (including older persons) and adolescents with cancer-related pain</td><td rowspan="7">Background:

Cancer-related neuropathic pain is common. It can be caused by the disease or due to acute or chronic effects of cancer treatment. Anti-depressants used in neuropathic pain treatment include tricyclic antidepressants (TCAs) and selective serotonin norepinephrine reuptake inhibitors (SNRIs). Evidence exists that might suggest their efficacy in neuropathic pain.[152]

Current WHO recommendation:

• As with nociceptive pain, pharmacotherapy is the mainstay of management for neuropathic pain. One or more of the following groups of medications may help:
○ Tricyclic antidepressants
○ Anticonvulsants
○ Local anaesthetic congeners (class I anti-arrhythmics)
• Patients with neuropathic pain may derive benefit from opioids, particularly in cases of nerve compression. However, nerve compression pain may respond only if a corticosteroid is added. Mixed nociceptive and neuropathic pain will also benefit from morphine. Superficial burning pain and spontaneous stabbing pain associated with nerve injury often responds best to a tricyclic antidepressant or an anticonvulsant.
• With regard to tricyclic antidepressants- Amitriptyline and imipramine are both widely available. Alternative preparations are available in many countries and may be more suitable for some patients. Nortriptyline does not have a sedative effect; desipramine is relatively non-sedative and has minimal anticholinergic.
The starting dose will depend on the patient's age, weight, previous use of such medications and concurrent medication. A dose as low as 10mg may be appropriate for some patients, but most can take 25-50mg. The dose should be increased to 30-50mg as rapidly as can be tolerated in terms of sedation, postural hypotension and dry mouth. After that, increments should be made on a weekly basis until the pain is relieved or adverse</td></tr>
<tr><td>INTERVENTION:</td><td>Anti-depressants</td></tr>
<tr><td>COMPARISON:</td><td>Anti-depressants</td></tr>
<tr><td>MAIN OUTCOMES:</td><td>• Pain relief
• Pain relief speed
• Pain relief maintenance
• Quality of life (QoL)
• Functional outcomes
• Sedation (adverse event)
• Anxiety or tremor (adverse event)</td></tr>
<tr><td>STRATIFICATIONS:</td><td>• Age (adults, older persons, adolescents, children)
• History of substance abuse
• Refractory pain</td></tr>
<tr><td>SETTING:</td><td>All</td></tr>
<tr><td>PERSPECTIVE:</td><td>Population</td></tr>
</table>

		effects preclude further escalation. Except with nortriptyline, the total daily dose should be given at bedtime, because most tricyclic antidepressants have a sedative effect. An analgesic effect is seen in many patients after a few days on doses of 50-100mg. The pain is always completely relieved.

	CRITERIA	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	**Research evidence** Cancer-related neuropathic pain is common. It can be caused by the disease or due to acute or chronic effects of cancer treatment. Anti-depressants used in neuropathic pain treatment include tricyclic antidepressants (TCAs) and selective serotonin norepinephrine reuptake inhibitors (SNRIs). Some evidence exists to suggests their efficacy in neuropathic pain[152]. WHO should issue updated guidance on their use. **Additional considerations** None

BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Yes ☐ No ☐ Uncertain ☒ Yes	• **No randomized controlled trials** compared anti-depressants to other anti-depressants **BENEFITS and HARMS** • **No trial** reported on **pain relief**. • **No trial** reported on **pain relief speed**. • **No trial** reported on **pain relief maintenance**. • **No trial** reported on **QoL**. • **No trial** reported on **functional outcomes**. • **No trial** reported on **sedation**. • **No trial** reported on **anxiety or tremor**. **STRATIFICATIONS** • Studies conducted in adults with a wide age range, without stratification into adolescent, non-older persons, and older persons. • Studies provide no data regarding history of substance abuse. • Studies provide no data regarading refractory pain. **SUMMARY** No eligible trials were found that address this sub-question.

ACCEPTABILITY & PREFERENCES	**Is there important uncertainty or variability about how much people value the options?** Major variability [ ] Minor variability [ ] Uncertain [Yes] **Is the option acceptable to key stakeholders?** Yes [ ] No [ ] Uncertain [Yes]	**<u>Research evidence</u>** None **<u>Additional considerations</u>** None

FEASIBILITY ./ RESOURCE USE	**How large are the resource requirements?** Major Minor Uncertai ☐ ☐ Yes **Is the option feasible to implement?** Yes No Uncertain ☐ ☐ Yes	**Research evidence** None **Additional considerations** None
	Would the option improve equity in health? Yes No Uncertai ☐ ☐ Yes	**Research evidence** None **Additional considerations** None

Recommendation	**Current recommendation:** As with nociceptive pain, pharmacotherapy is the mainstay of management for neuropathic pain. One or more of the following groups of medications may help: • Tricyclic antidepressants • Anticonvulsants • Local anaesthetic congeners (class I anti-arrhythmics) Patients with neuropathic pain may derive benefit from opioids, particularly in cases of nerve compression. However, nerve compression pain may respond only if a corticosteroid is added. Mixed nociceptive and neuropathic pain will also benefit from morphine. Superficial burning pain and spontaneous stabbing pain associated with nerve injury often responds best to a tricyclic antidepressant or an anticonvulsant. With regard to tricyclic antidepressants- Amitriptyline and imipramine are both widely available. Alternative preparations are available in many countries and may be more suitable for some patients. Nortriptyline does not have a sedative effect; desipramine is relatively non-sedative and has minimal anticholinergic. The starting dose will depend on the patient's age, weight, previous use of such medications and concurrent medication. A dose as low as 10mg may be appropriate for some patients, but most can take 25-50mg. The dose should be increased to 30-50mg as rapidly as can be tolerated in terms of sedation, postural hypotension and dry mouth. After that, increments should be made on a weekly basis until the pain is relieved or adverse effects preclude further escalation. Except with nortriptyline, the total daily dose should be given at bedtime, because most tricyclic antidepressants have a sedative effect. An analgesic effect is seen in many patients after a few days on doses of 50-100mg. The pain is always completely relieved. In children, the recommended starting dose is 0.5 mg/kg of body weight, increasing to 1 mg/kg if necessary. **New (draft) recommendation:** None

Strength of Recommendation	
Quality of Evidence	➢ None [Omitted for no data]
Justification	The GDG could not make a recommendation for one antidepressant over others due to lack of evidence.
Subgroup considerations	
Implementation considerations [incl. M&E]	
Research priorities	

5.4. In adults (including older persons) and adolescents with cancer-related neuropathic pain, what is the evidence for the use of second generation anti-epileptics such as gabapentin or first generation anti-epileptics such as carbamezapine or sodium valproate compared with placebo, no anti-epileptic, or other antiepileptics in order to achieve rapid, effective and safe pain control?

The systematic review team have divided Key Question 5.4 into two sections: anti-epileptics versus placebo and comparisons of anti-epileptics.

5.4.1. Anti-Epileptics vs. Placebo

Four eligible studies compared anti-epileptics to placebo (see Evidence Profile 5.4.1).[153-156] Two evaluated pregabalin, one gabapentin, and one both pregabalin and gabapentin. Each study included participants with a variety of cancers. Study participants were of a range of ages, with average ages ranging from 57 to 66 years.

A single trial provides low strength of evidence regarding the likelihood of relieving pain with an anti-epileptic compared with placebo (RR = 1.48; 95% CI 0.82 to 2.67) and that anti-epileptics reduce pain severity (difference between groups of -4.4 [95% CI -8.3, -0.5] on a transformed 0 to 100 [worst] scale).

No studies evaluated speed of pain relief, pain relief duration, quality of life, or functional outcomes. Three of the studies provided high strength of evidence of more than a three-fold increase in the risk of sedation (somnolence or drowsiness) with anti-epileptics (RR = 3.66; 95% CI 1.96, 6.85).

Evidence Profile 5.4.1. Anti-Epileptics vs. Placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Anti-Epileptics**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Pain relief (categorical) (follow up: 28 days)												
1 [1]	RCT	serious [A]	not serious	N/A	serious [B]	single study	20/72 (28%)	15/80 (19%)	**RR 1.48** (0.82 to 2.67)	**90 more per 1000** (from 33 fewer to 313 more)	Low	CRITICAL
Pain relief (continuous) (follow up: range 4 weeks to 6 months; assessed with: VAS; Scale: 0 to 100 [worst] [C])												
4 [1,2,3,4]	RCT	very serious [D]	not serious	not serious	not serious	none	189	160	**Diff -4.4** (-8.3, -0.5) [C]		Low	CRITICAL
Pain relief speed												
0									not estimable			CRITICAL
Pain reduction maintenance												
0									not estimable			CRITICAL
Quality of life												
0									not estimable			IMPORTANT
Functional outcomes												
0									not estimable			IMPORTANT
Adverse events: Sedation (somnolence or drowsiness, follow-up 4 weeks to 6 months)												
3 [1,5,6]	RCT	not serious	not serious	not serious	not serious	none	39/142 (28% [E])	11/150 (8.0% [E])	**RR 3.66 (1.96, 6.85)**	**213 more per 1000** (from 77 to 468 more)	High	IMPORTANT
Adverse events: Confusion (follow up: range 4 weeks to 6 months)												
0									not estimable			IMPORTANT

***Abbreviations**: **CI:** Confidence interval; **Diff:** difference (between groups); **N/A:** not applicable; **NS:** nonsignificant; **OR:** Odds ratio; **RCT:** randomized control trial(s); **VAS**: Visual Analog Scale.*

Explanations

A. Study had significant issues with enrollment and was terminated early.
B. Small sample size.
C. Scales transformed to 0 to 100, as necessary.
D. One study had significant issues with enrollment and was terminated early. Incomplete reporting of either within-group differences or final values in studies diminishes the interpretation of the results across studies.
E. Meta-analyzed value.

Trials

1. Sjolund, K. F., Yang, R., Lee, K. H., Resnick, M. Randomized study of pregabalin in patients with cancer-induced bone pain. Pain Ther; Jun 2013.
2. Mishra, S., Bhatnagar, S., Goyal, G. N., Rana, S. P., Upadhya, S. P. A comparative efficacy of amitriptyline, gabapentin, and pregabalin in neuropathic cancer pain: a prospective randomized double-blind placebo-controlled study. Am J Hosp Palliat Care; May 2012.
3. Rao, R. D., Michalak, J. C., Sloan, J. A., Loprinzi, C. L., Soori, G. S., Nikcevich, D. A., et al. Efficacy of Gabapentin in the Management of Chemotherapy-induced Peripheral Neuropathy: A Phase 3 Randomized, Double-Blind, Placebo-controlled, Crossover Trial (N00C3). Cancer; Nov 2007.
4. Caraceni, A., Zecca, E., Bonezzi, C., Arcuri, E., Yaya Tur, R., Maltoni, M., et al. Gabapentin for Neuropathic Cancer Pain: A Randomized Controlled Trial From the Gabapentin Cancer Pain Study Group. J Clin Oncol; 2004
5. Dou, Z., Jiang, Z., Zhong, J. Efficacy and safety of pregabalin in patients with neuropathic cancer pain undergoing morphine therapy. Asia Pac J Clin Oncol; Apr 2017.
6. Chen, D. L., Li, Y. H., Wang, Z. J., Zhu, Y. K. The research on long-term clinical effects and patients' satisfaction of gabapentin combined with oxycontin in treatment of severe cancer pain. Medicine (Baltimore); Oct 2016.

Evidence-to-Decision table 5.4.1		
In adults (including older persons) and adolescents with cancer-related neuropathic pain, what is the evidence for the use of second generation anti-epileptics or first generation anti-epileptics such as carbamezapine or sodium valproate compared to placebo in order to achieve pain control?		
POPULATION:	Adults (including older persons) and adolescents with cancer-related pain	**Background:** Cancer-related neuropathic pain is common. It can be caused by the disease or due to acute or chronic effects of cancer treatment. Certain antiepileptics are reported to be effective for treatment of neuropathic pain[152], including gabapentin, pregabalin, carbamazepine and valproate. Gabapentin is widely used and was considered for inclusion on WHO EML for neuropathic pain but was not included because of its uncertain benefits. Additional evidence cited in the Technical Report Series for the EML 2017 (but not included in the application) recounted the following history, quoted from [157] in full: *'In 1993, gabapentin (Neurontin®, Pfizer) was first approved by the U.S. Food & Drug Administration (FDA) as an adjunctive therapy for epilepsy. In 2002, the drug was approved for the management of post-herpetic neuralgia, its only pain-related indication.* *Parke-Davis and Pfizer, the companies responsible for promoting and marketing gabapentin, adopted a publication strategy "to disseminate the information as widely as possible through the world's medical literature"[158]. This promotion was judged to be illegal and fraudulent: in 2004, American pharmaceutical manufacturer Warner-Lambert pleaded guilty and agreed to pay more than US$ 430 million to resolve criminal charges and civil liabilities in connection with its Parke-Davis division's marketing scheme of unapproved uses of gabapentin[159]. This was one of the largest settlements reached between the United States Department of Justice and pharmaceutical companies.* *Following litigation, internal company documents relating to gabapentin publication strategy have been made publicly available through two separate legal actions[160,161]. These sources were analysed in a series of studies [162-165] that documented publication and outcome reporting biases and data manipulation. The magnitude of these biases is highly relevant, and affects the evidence presented in the application. Firstly, in 2009, of 20 clinical trials for*
INTERVENTION:	Anti-epileptics	
COMPARISON:	Placebo (no treatment)	
MAIN OUTCOMES:	• Pain relief • Pain relief speed • Pain relief maintenance • Quality of life (QoL) • Functional outcomes • Sedation (adverse event) • Confusion (adverse event)	
STRATIFICATIONS:	• Age (adults, older persons, adolescents, children) • History of substance abuse • Refractory pain	
SETTING:	All	
PERSPECTIVE:	Population	

		which internal documents were available from Pfizer and Parke-Davis, eight were never published. Secondly, there were irreconcilable differences between the original protocols, statistical analysis plans, interim research reports and the main publications relating to most trials. For eight of the 12 published trials, the primary outcome defined in the published report differed from that described in the protocol. In three out of 10 trials, the numbers of participants randomized and analysed for the primary outcome and the type of analysis for efficacy and safety in the internal research report and the trial publication differed. Different subsets of participants were included in the analysis, leading to different findings: in one trial, the main findings in the publication did not include data from 40% of participants actually randomized. These changes are likely to have unbalanced the comparisons, favouring responsive patients and excluding poor responders in the arms allocated to gabapentin, thereby inflating the size of the effect attributable to the drug. *The important differences between the internal and published documents about the number of patients or the plans of the analyses invalidate the study design (i.e. downgrading the evidence from experimental to observational), as the randomization is no longer valid.'* **Current WHO recommendation**: As with nociceptive pain, pharmacotherapy is the mainstay of management for neuropathic pain. One or more of the following groups of medications may help: • Tricyclic antidepressants • Anticonvulsants • Local anesthetic congeners (class I antiarrhythmics) Patients with neuropathic pain may derive benefit from opioids, particularly in cases of nerve compression. However, nerve compression pain may respond only if a corticosteroid is added. Mixed nociceptive and neuropathic pain will also benefit from morphine. Superficial burning pain and spontaneous stabbing pain associated with nerve injury often responds best to a tricyclic antidepressant or an antiepileptic.

		With regard to antiepileptics, extensive clinical experience supports the use of anticonvulsants such as carbamazepine and valproic acid in the treatment of nerve injury pain, particularly stabbing pain. The starting dose of carbamazepine is 100mg twice daily. This can be increased slowly, at a rate of 200mg every few days. Carbamazepine causes enzyme autoinductionf. thereby enhancing its own metabolism. This is one reason why initial adverse effects (e.g. drowsiness, ataxia) improve with time. Carbamazepine occasionally causes leukopenia. Carbamazepine may exacerbate pre-existing chemotherapy-induced suppression of bone marrow. *[This medication should not be used in children under six years of age. In older children, start by giving 100mg/day (2—3 mg/kg of body weight), and increase in stages to 500mg/day it necessary.]* Valproic acid has a long plasma half-life and is sedative. It may conveniently be given as a single dose at bedtime, at a starting dose of 500 mg, or 200mg for older persons. The dose may be increased by 200mg, if necessary, every 3-4 days to a maximum of 1—1.5g. As the medication accumulates in the body, the dose may subsequently have to be reduced. *[Valproic acid should not be used in children under two years of age because of the danger of hepatotoxicity, which may be fatal.]*

	CRITERIA	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** Yes	**Research evidence** Cancer-related neuropathic pain is common. It can be caused by the disease or due to acute or chronic effects of cancer treatment. Certain antiepileptics are reported to be effective for treatment of neuropathic pain[152], although some of the evidence for gabapentin in now disputed (see 'Background' section for this question). **Additional considerations** None

BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Yes: ☐ No: ☐ Uncertain: ☒ Yes	• **Four randomized controlled trials** compared anti-epileptics to placebo Two evaluated pregabalin, one gabapentin, and one both pregabalin and gabapentin. Each study included participants with a variety of cancers. **BENEFITS and HARMS** • **One trial** provided **low strength of evidence** an **increased likelihood of relieving pain with an anti-epileptic compared to placebo** (RR = 1.48; 95% CI 0.82 to 2.67) and that anti-epileptics reduce pain severity (difference between groups of -4.4 [95% CI -8.3, -0.5] on a transformed 0 to 100 [worst] scale). • **No trial** reported on **pain relief speed**. • **No trial** reported on **pain relief maintenance**. • **No trial** reported on **QoL**. • **No trial** reported on **functional outcomes**. • **Three trials** provided **high strength of evidence** of **more than a three-fold increase in the risk of sedation (somnolence or drowsiness) with anti-epileptics** (RR = 3.66; 95% CI 1.96, 6.85). • **No trial** reported on **confusion**. **STRATIFICATIONS** • Studies conducted in adults with a wide age range, without stratification into adolescent, non-older persons, and older persons. • Studies provide no data regarding history of substance abuse. • Studies provide no data regarading refractory pain. **SUMMARY** Anti-epileptics may result in greater pain relief, but increase the risk of sedation. However, the findings of the review are called into doubt in light of the presentation of the evidence quoted in the 'Background' section of this question.

ACCEPTABILITY & PREFERENCES	**Is there important uncertainty or variability about how much people value the options?** Major variability [ ] Minor variability [ ] Uncertain [Yes] **Is the option acceptable to key stakeholders?** Yes [ ] No [ ] Uncertain [Yes]	**Research evidence** None **Additional considerations** None

FEASIBILITY ./ RESOURCE USE	**How large are the resource requirements?** Major Minor Uncertai ☐ ☐ Yes **Is the option feasible to implement?** Yes No Uncertain ☐ ☐ Yes	**Research evidence** None **Additional considerations** None
	Would the option improve equity in health? Yes No Uncertai ☐ ☐ Yes	**Research evidence** None **Additional considerations** None

Recommendation	**Current recommendation:** As with nociceptive pain, pharmacotherapy is the mainstay of management for neuropathic pain. One or more of the following groups of medications may help: • Tricyclic antidepressants • Anticonvulsants • Local anesthetic congeners (class I antiarrhythmics) Patients with neuropathic pain may derive benefit from opioids, particularly in cases of nerve compression. However, nerve compression pain may respond only if a corticosteroid is added. Mixed nociceptive and neuropathic pain will also benefit from morphine. Superficial burning pain and spontaneous stabbing pain associated with nerve injury often responds best to a tricyclic antidepressant or an antiepileptic. With regard to antiepileptics, extensive clinical experience supports the use of anticonvulsants such as carbamazepine and valproic acid in the treatment of nerve injury pain, particularly stabbing pain. The starting dose of carbamazepine is 100mg twice daily. This can be increased slowly, at a rate of 200mg every few days. Carbamazepine causes enzyme autoinduction. thereby enhancing its own metabolism. This is one reason why initial adverse effects (e.g. drowsiness, ataxia) improve with time. Carbamazepine occasionally causes leukopenia. Carbamazepine may exacerbate pre-existing chemotherapy-induced suppression of bone marrow. *[This medication should not be used in children under six years of age. In older children, start by giving 100mg/day (2—3 mg/kg of body weight), and increase in stages to 500mg/day it necessary.]* Valproic acid has a long plasma half-life and is sedative. It may conveniently be given as a single dose at bedtime, at a starting dose of 500 mg, or 200mg for older persons. The dose may be increased by 200mg, if necessary, every 3-4 days to a maximum of 1—1.5g. As the medication accumulates in the body, the dose may subsequently have to be reduced. *[Valproic acid should not be used in children under two years of age because of the danger of hepatotoxicity, which may be fatal.]* **New (draft) recommendation:** None

Strength of Recommendation	None
Quality of Evidence	➢ **LOW** [Pain (critical) = low Sedation (important) = high others omitted for no data]
Justification	The findings of the review were called into doubt in light of fraudulent gabapentin data, discussed in the 'Background' section of this question, which the GDG were alerted to at the guideline formulation meeting. This revelation prevented a recommendation from being made due to lack of evidence.
Subgroup considerations	
Implementation considerations [incl. M&E]	
Research priorities	

5.4.2. Comparisons of Anti-Epileptics

A single study compared anti-epileptics (see Evidence Profile 5.4.2 below).[153] The trial compared pregabalin and gabapentin (in addition to placebo and amitriptyline) among patients with cancer-related neuropathic pain. Age, sex, and other demographics of the study population were not reported. Regarding outcomes of interest the study reported only that participants who received pregabalin had a greater reduction in their pain on a visual analog scale than those who received gabapentin, providing very low strength of evidence. The net difference in pain scores (transformed to 0 to 100 [worst] scale) between arms was -8.4 (95% CI -16.5, -0.3).

Evidence Profile 5.4.2. Comparison of Anti-Epileptics

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pregabalin	Gabapentin	Relative (95% CI)	Absolute (95% CI)		
Pain relief (categorical)												
0									not estimable			CRITICAL
Pain relief (continuous) (follow up: 4 weeks; assessed with: VAS; Scale: 0 to 100 [worst] [A])												
1 [1]	RCT	not serious	N/A	not serious	serious [B]	single study	30	30	**Net Diff -8.4** (-16.5, -0.3)		Low	CRITICAL
Pain relief speed												
0									not estimable			CRITICAL
Pain reduction maintenance												
0									not estimable			CRITICAL
Quality of life												
0									not estimable			IMPORTANT
Functional outcomes												
0									not estimable			IMPORTANT
Adverse events: Sedation												
0									not estimable			IMPORTANT
Adverse events: Confusion												
0									not estimable			IMPORTANT

Abbreviations: CI: *Confidence interval;* ***N/A:*** *not applicable;* ***Net Diff:*** *net difference (between groups);* ***VAS****: Visual Analog Scale.*

Explanations

A. Scales transformed to 0 to 100, as necessary.
B. Small study.

Trials

1. Mishra, S., Bhatnagar, S., Goyal, G. N., Rana, S. P., Upadhya, S. P.. A comparative efficacy of amitriptyline, gabapentin, and pregabalin in neuropathic cancer pain: a prospective randomized double-blind placebo-controlled study. Am J Hosp Palliat Care; May 2012.

Evidence-to-Decision table 5.4.2		
In adults (including older persons) and adolescents with cancer-related neuropathic pain, what is the evidence for the use of second generation anti-epileptics or first generation anti-epileptics such as carbamezapine or sodium valproate compared other anti-epileptics in order to achieve pain control?		
POPULATION:	Adults (including older persons) and adolescents with cancer-related pain	**Background:** Cancer-related neuropathic pain is common. It can be caused by the disease or due to acute or chronic effects of cancer treatment. Certain antiepileptics are reported to be effective for treatment of neuropathic pain[152], including gabapentin, pregabalin, carbamazepine and valproate. Gabapentin is widely used and was considered for inclusion on WHO EML for neuropathic pain but was not included because of its uncertain benefits. Additional evidence cited in the Technical Report Series for the EML 2017 (but not included in the application) recounted the following history, quoted from [157] in full: *'In 1993, gabapentin (Neurontin®, Pfizer) was first approved by the U.S. Food & Drug Administration (FDA) as an adjunctive therapy for epilepsy. In 2002, the drug was approved for the management of post-herpetic neuralgia, its only pain-related indication.* *Parke-Davis and Pfizer, the companies responsible for promoting and marketing gabapentin, adopted a publication strategy "to disseminate the information as widely as possible through the world's medical literature"[158]. This promotion was judged to be illegal and fraudulent: in 2004, American pharmaceutical manufacturer Warner-Lambert pleaded guilty and agreed to pay more than US$ 430 million to resolve criminal charges and civil liabilities in connection with its Parke-Davis division's marketing scheme of unapproved uses of gabapentin[159]. This was one of the largest settlements reached between the United States Department of Justice and pharmaceutical companies.* *Following litigation, internal company documents relating to gabapentin publication strategy have been made publicly available through two separate legal actions[160,161]. These sources were analysed in a series of studies [162-165] that documented publication and outcome reporting biases and data manipulation. The magnitude of these biases is highly relevant,*
INTERVENTION:	Anti-epileptics	
COMPARISON:	Anti-epileptics	
MAIN OUTCOMES:	• Pain relief • Pain relief speed • Pain relief maintenance • Quality of life (QoL) • Functional outcomes • Sedation (adverse event) • Confusion (adverse event)	
STRATIFICATIONS:	• Age (adults, older persons, adolescents, children) • History of substance abuse • Refractory pain	
SETTING:	All	
PERSPECTIVE:	Population	

		and affects the evidence presented in the application. Firstly, in 2009, of 20 clinical trials for which internal documents were available from Pfizer and Parke-Davis, eight were never published. Secondly, there were irreconcilable differences between the original protocols, statistical analysis plans, interim research reports and the main publications relating to most trials. For eight of the 12 published trials, the primary outcome defined in the published report differed from that described in the protocol. In three out of 10 trials, the numbers of participants randomized and analysed for the primary outcome and the type of analysis for efficacy and safety in the internal research report and the trial publication differed. Different subsets of participants were included in the analysis, leading to different findings: in one trial, the main findings in the publication did not include data from 40% of participants actually randomized. These changes are likely to have unbalanced the comparisons, favouring responsive patients and excluding poor responders in the arms allocated to gabapentin, thereby inflating the size of the effect attributable to the drug. *The important differences between the internal and published documents about the number of patients or the plans of the analyses invalidate the study design (i.e. downgrading the evidence from experimental to observational), as the randomization is no longer valid.'* **Current WHO recommendation**: As with nociceptive pain, pharmacotherapy is the mainstay of management for neuropathic pain. One or more of the following groups of medications may help: • Tricyclic antidepressants • Anticonvulsants • Local anaesthetic congeners (class I anti-arrhythmics) Patients with neuropathic pain may derive benefit from opioids, particularly in cases of nerve compression. However, nerve compression pain may respond only if a corticosteroid is added. Mixed nociceptive and neuropathic pain will also benefit from morphine. Superficial burning pain and spontaneous stabbing pain associated with nerve injury often responds best to a tricyclic antidepressant or an antiepileptic.

		With regard to anti-epileptics, extensive clinical experience supports the use of anticonvulsants such as carbamazepine and valproic acid in the treatment of nerve injury pain, particularly stabbing pain. The starting dose of carbamazepine is 100mg twice daily. This can be increased slowly, at a rate of 200mg every few days. Carbamazepine causes enzyme auto-induction, thereby enhancing its own metabolism. This is one reason why initial adverse effects (e.g. drowsiness, ataxia) improve with time. Carbamazepine occasionally causes leukopenia. Carbamazepine may exacerbate pre-existing chemotherapy-induced suppression of bone marrow. *[This medication should not be used in children under six years of age. In older children, start by giving 100mg/day (2—3 mg/kg of body weight), and increase in stages to 500mg/day it necessary.]* Valproic acid has a long plasma half-life and is sedative. It may conveniently be given as a single dose at bedtime, at a starting dose of 500 mg, or 200mg for older persons. The dose may be increased by 200mg, if necessary, every 3-4 days to a maximum of 1—1.5g. As the medication accumulates in the body, the dose may subsequently have to be reduced. *[Valproic acid should not be used in children under two years of age because of the danger of hepatotoxicity, which may be fatal.]*

	CRITERIA	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** Yes	**Research evidence** Cancer-related neuropathic pain is common. It can be caused by the disease or due to acute or chronic effects of cancer treatment. Certain anti-epileptics are reported to be effective for treatment of neuropathic pain[152], although some of the evidence for gabapentin in now disputed (see 'Background' section for this question). **Additional considerations** None

BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Yes: ☐ No: ☐ Uncertain: ☒ Yes	• **One randomized controlled trial** compared anti-epileptics. The **trial compared pregabalin and gabapentin** among patients with cancer-related neuropathic pain. Demographic characteristics such as age were not reported in the trial. **BENEFITS and HARMS** • **One trial** provided **low strength of evidence** that **pain relief was greater in patients taking pregabalin than gabapentin**. The net difference in pain scores (transformed to 0 to 100 [worst] scale) between arms was -8.4 (95% CI -16.5, -0.3). • **No trial** reported on **pain relief speed**. • **No trial** reported on **pain relief maintenance**. • **No trial** reported on **QoL**. • **No trial** reported on **functional outcomes**. • **No trial** reported on **sedation**. • **No trial** reported on **confusion**. **STRATIFICATIONS** • Studies conducted in adults with a wide age range, without stratification into adolescent, non-older persons, and older persons. • Studies provide no data regarding history of substance abuse. • Studies provide no data regarading refractory pain. **SUMMARY** Pregabalin may improve pain relief.

ACCEPTABILITY & PREFERENCES	**Is there important uncertainty or variability about how much people value the options?** Major variability [ ] Minor variability [ ] Uncertain [Yes] **Is the option acceptable to key stakeholders?** Yes [ ] No [ ] Uncertain [Yes]	**<u>Research evidence</u>** None **<u>Additional considerations</u>** None

FEASIBILITY ./ RESOURCE USE	**How large are the resource requirements?** Major ☐ Minor ☐ Uncertai Yes **Is the option feasible to implement?** Yes ☐ No ☐ Uncertain Yes	**Research evidence** None **Additional considerations** None
	Would the option improve equity in health? Yes ☐ No ☐ Uncertai Yes	**Research evidence** None **Additional considerations** None

Recommendation	**Current recommendation:** As with nociceptive pain, pharmacotherapy is the mainstay of management for neuropathic pain. One or more of the following groups of medications may help: • Tricyclic antidepressants • Anticonvulsants • Local anaesthetic congeners (class I anti-arrhythmics) Patients with neuropathic pain may derive benefit from opioids, particularly in cases of nerve compression. However, nerve compression pain may respond only if a corticosteroid is added. Mixed nociceptive and neuropathic pain will also benefit from morphine. Superficial burning pain and spontaneous stabbing pain associated with nerve injury often responds best to a tricyclic antidepressant or an antiepileptic. With regard to anti-epileptics, extensive clinical experience supports the use of anticonvulsants such as carbamazepine and valproic acid in the treatment of nerve injury pain, particularly stabbing pain. The starting dose of carbamazepine is 100mg twice daily. This can be increased slowly, at a rate of 200mg every few days. Carbamazepine causes enzyme auto-induction, thereby enhancing its own metabolism. This is one reason why initial adverse effects (e.g. drowsiness, ataxia) improve with time. Carbamazepine occasionally causes leukopenia. Carbamazepine may exacerbate pre-existing chemotherapy-induced suppression of bone marrow. *[This medication should not be used in children under six years of age. In older children, start by giving 100mg/day (2—3 mg/kg of body weight), and increase in stages to 500mg/day it necessary.]* Valproic acid has a long plasma half-life and is sedative. It may conveniently be given as a single dose at bedtime, at a starting dose of 500 mg, or 200mg for older persons. The dose may be increased by 200mg, if necessary, every 3-4 days to a maximum of 1—1.5g. As the medication accumulates in the body, the dose may subsequently have to be reduced. *[Valproic acid should not be used in children under two years of age because of the danger of hepatotoxicity, which may be fatal.]* **New (draft) recommendation:** None

Strength of Recommendation	
Quality of Evidence	➢ **LOW** [Pain (critical) = low other outcomes omitted for no data]
Justification	The findings of the review were called into doubt in light of fraudulent gabapentin data, discussed in the 'Background' section of this question, which the GDG were alerted to at the guideline formulation meeting. This revelation prevented a recommendation from being made due to lack of evidence.
Subgroup considerations	
Implementation considerations [incl. M&E]	
Research priorities	

Key Question 6: Radiotherapy

6.1. In adults (including older persons) and adolescents with pain related to bone metastases, what is the evidence for the use of low-fractionated radiotherapy as compared with high-fractionated radiotherapy or radioisotopes in order to achieve rapid, effective and safe pain control?

Twenty-three eligible RCTs compared low-fractioned to high-fractioned radiotherapy.[166-189] Almost all used a single fractionation of 8 Gy in the low fractionation arms (two older studies used single fractionations of either 10 Gy or a range from 8 to 15 Gy; one study arm that used 5 Gy was omitted). High-fractionated radiotherapy ranged from 20 to 30 Gy mostly given over 5 to 10 fractions. These trials included patients with a variety of cancer types, with breast, prostate, and lung cancers included in most trials. Among trials that reported participant ages, study participants were mostly older adults; the mean age ranged from 48 to 72 years old, with the youngest participant being 16 years old.

Evidence Profile 6.1 summarizes the findings from the RCTs. There is high quality evidence that the different fractionation schedules were similarly effective in terms of producing pain relief ("complete response", Forest Plot 6.1.1 below) and improvement ("complete or partial response", Forest Plot 6.1.2 below). Under both schedules 25% or 26% of participants achieved complete pain relief (RR = 0.97; 95% CI 0.89, 1.06) and 69% or 71% of participants achieved either complete or partial pain relief (RR = 0.97; 95% CI 0.93, 0.998). Pain relief was infrequently reported on a continuous scale. Three trials provided low quality evidence of no difference between fractionation schedules. The trials could not be quantitatively combined, but all reported statistically non-significant differences.

Three studies reported on pain relief speed (time to complete response), providing moderate strength of no difference between radiotherapy schedules; however, all studies reported outcomes vaguely, either as survival curves showing nonsignificant differences or that pain relief was achieved in two weeks in both study arms. Nine studies reported on duration of pain relief (pain reduction maintenance), providing moderate quality evidence of no difference between radiotherapy schedules. Most studies reported only no significant difference between radiotherapy schedules; one trial reported a HR = 0.91 (95% CI 0.46, 1.82).

There is high quality evidence that pathological fractures at the treatment (index) site are more common with low-fractionated than high-fractionated radiotherapy (Forest Plot 6.1.3 below). Across studies about 3% to 4% of patients had a pathological fracture at the index site and the RR = 1.48 (95% CI 1.08, 2.03). There is also high quality evidence that spinal cord compression (among those treated for spinal metastases) are more common with low-fractionated (2.2%) than high-fractionated radiotherapy (1.4%); although the difference was not statistically significant (Forest Plot 6.1.4 below). Across studies, the RR = 1.45; 95% CI 0.89, 2.37).

Three trials provided low quality evidence of no significant differences in improvements in quality of life (RR = 1.02; 95% CI 0.83, 1.26, or no difference in change in score). Four trials provided low quality evidence of no significant differences in improvements in physical function (RR = 1.11; 95% CI 0.84, 1.46). Mean difference -0.6 months until improvement (95% CI -2.8, 1.6). One trial provided very low quality evidence of no significant difference in social function (RR = 0.98; 95% CI 0.80, 1.20). One trial provided very low quality evidence of more acute bone flares with single fractionated than multiple fractionated radiotherapy (RR = 3.45; 95% CI 0.73, 16.3).

Evidence Profile 6.1. Single Fractionated vs. Multiple Fractionated Radiotherapy

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Single fractionated**	**Multiple fractionated**	**Relative (95% CI)**	**Absolute (95% CI)**		
Pain relief (categorical) (complete response, follow up: range 1 to 12 months)												
18 [1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18]	RCT	not serious	not serious	not serious	not serious	none	568/2232 (25.4%)	562/2178 (25.8%	**RR 0.97** (0.89, 1.06)	**8 fewer per 1000** (from 28 fewer to 15 more)	High	CRITICAL
Pain relief (categorical) (improvement [complete or partial response], follow up: range 1 to 12 months)												
21 [1,2,3,4,5,6,7,8,9,10,11,12,13,14,16,17,18,19,20,21,22]	RCT	not serious	not serious	not serious	not serious	none	1588/2312 (68.7%)	1673/2341 (71.5%)	**RR 0.97** (0.93, 0.998)	**21 fewer per 1000** (from 48 to 1 fewer)	High	CRITICAL
Pain relief (continuous) (follow up: range 1 to 11 months; assessed with: VAS, NRS; Scale: 0 to 100 [worst] [A])												
3 [2,7,22]	RCT	not serious	not serious	not serious	serious [B]	Insufficient data for analysis	125	133	**HR 0.99** (0.51, 1.91) **Diff -5 to 2.5** (NS)		Low	CRITICAL
Pain relief speed												
3 [5,7,23]	RCT	not serious	not serious	not serious	serious [C]	none	597	598	NS [C]		Moderate	CRITICAL
Pain reduction maintenance												
9 [4,7,8,9,10,14,15,16,18]	RCT	not serious	not serious	not serious	not serious	Insufficient data for analysis	1201	1192	**HR 0.91** (0.46, 1.82) [D] **Diff 0 to -2 mo** [D] (NS)		Moderate	CRITICAL
Skeletal-related events (Fracture at index site, follow up: range 1 to 12 months)												
10 [5,6,9,10,11,14,15,16,19,24]	RCT	not serious	not serious	not serious	not serious	none	97/2185 (4.4%)	64/2178 (2.9%)	**RR 1.48** (1.08, 2.03)	**21 more per 1000** (from 4 to 46 more)	High	IMPORTANT
Skeletal-related events (Spinal cord compression at index site, follow up: range 2 to 12 months)												
8 [1,5,6,9,15,16,21,24]	RCT	not serious	not serious	not serious	not serious	none	38/1763 (2.2%)	25/1796 (1.4%)	**RR 1.45** (0.89, 2.37)	**10 more per 1000** (from 2 fewer to 30 more)	High	IMPORTANT
Quality of life: Improved (follow up: 1-2 months; assessed with: QLQ-C30 Global, Spitzer Index, Global QoL)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Single fractionated**	**Multiple fractionated**	**Relative (95% CI)**	**Absolute (95% CI)**		
3 [6,8,14]	RCT	not serious	not serious	very serious [E]	not serious	none	118/336 (35%) improved 129 (continuous measure)	115/335 (34%) improved 111 continuous	**RR 1.02** (0.83, 1.26) **Diff 0** (nd)	**8 more per 1000** (from 58 fewer to 89 more)	Low	IMPORTANT
Functional outcomes: Physical, improved (follow up: 1.5-6 months; assessed with: QLQ-C30 Physical, Karnofsky performance status, Barthel index of ADL, "Performance status")												
4 [6,9,19,22]	RCT	not serious	not serious	very serious [F]	not serious	none	111/270 (41%) improved 45 (continuous measure)	116/293 (40%) improved 45 (continuous measure)	**RR 1.11** (0.84, 1.46) **Diff -0.6 mo** (-2.8, 1.6)	**43 more per 1000** (from 63 fewer to 182 more)	Low	IMPORTANT
Functional outcomes: Social, improved (follow up: 2 months; assessed with: QLQ-C30 social)												
1 [6]	RCT	not serious	N/A	very serious [G]	not serious	single study	101/232 (44%)	106/238 (45%)	**RR 0.98** (0.80, 1.20)	**10 fewer per 1000** (from 88 more to 90 fewer)	Very Low	IMPORTANT
Adverse events: Acute bone flare (severe flare, follow-up: 2 months)												
1 [16]	RCT	not serious	N/A	not serious	serious [H]	single study	7/137 (5.1%)	2/135 (1.5%)	**RR 3.45** (0.73, 16.3)	**36 more per 1000** (from 6 fewer to 78 more)	Very Low	IMPORTANT

***Abbreviations: CI**: confidence interval; **Diff**: difference (between groups); **EORTC**: European Organisation for Research and Treatment of Cancer; **GI**: gastrointestinal; **N/A**: not applicable; **NS**: not statistically significant; **NRS**: Numeric Rating Scale; **RCT**: randomized controlled trial(s); **RR**: relative risk (log scale); **VAS**: Visual Analog Scale.*

Explanations

A. Scales transformed to 0 to 100, as necessary.
B. Single study reported hazard ratio; Others report means or medians and "nonsignificant" difference.
C. Bone Pain Trial Working Party 1999: logrank difference P = 0.6; Foro Arnalot 2008: logrank difference P = 0.48; Meeuse 2010: 2 vs 2 weeks P=0.54.
D. Hazard ratio reported in one study (Roos 2005). All trials, explicitly or implicitly, reported no significant difference in duration but with insufficient data to allow meta-analysis.
E. QLQ-C30 and Spitzer Index are measures of quality of life that mix concepts of both quality of life and functional outcomes. "Global QoL" was undefined.
F. Karnofsky and Barthel Index are measures of functional status that mix concepts of both quality and functional outcomes. "Performance status" was undefined,
F. QLQ-C30 is a measure of functional status that mix concepts of both quality and functional outcomes.
H. Fewer than 300 participants.

References

1. Altundağ MB, Üçer AR, Çalikoğlu, Guran Z. Single (500 CGY, 800 CGY) and multifraction (300X10 CGY) radiotherapy schedules in the treatment of painful bone metastases. International Journal of Hematology and Oncology. 2002;27(4):016-21.
2. Amouzegar-Hashemi F, Behrouzi H, Kazemian A, Zarpak B, Haddad P. Single versus multiple fractions of palliative radiotherapy for bone metastases: a randomized clinical trial in Iranian patients. Current oncology (Toronto, Ont). 2008;15(3):151.
3. Anter AH. Single Fraction versus Multiple Fraction Radiotherapy for treatment of painful bone metastases: a Prospective Study; Mansoura experience. Forum of Clinical Oncology; 2015: De Gruyter Open.

4. Badzio A, Senkus-Konefka E, Jereczek-Fossa BA, Adamska K, Fajndt S, Tesmer-Laskowska I, et al. 20 Gy in five fractions versus 8 Gy in one fraction in palliative radiotherapy of bone metastases. A multicenter randomized study. Nowotwory Journal of Oncology. 2003;53(3):261-.
5. Bone Pain Trial Working Party. 8 Gy single fraction radiotherapy for the treatment of metastatic skeletal pain: randomised comparison with a multifraction schedule over 12 months of patient follow-up. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 1999;52(2):111-21.
6. Chow E, van der Linden YM, Roos D, Hartsell WF, Hoskin P, Wu JS, et al. Single versus multiple fractions of repeat radiation for painful bone metastases: a randomised, controlled, non-inferiority trial. The Lancet Oncology. 2014;15(2):164-71.
7. Foro Arnalot P, Fontanals AV, Galceran JC, Lynd F, Latiesas XS, de Dios NR, et al. Randomized clinical trial with two palliative radiotherapy regimens in painful bone metastases: 30 Gy in 10 fractions compared with 8 Gy in single fraction. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2008;89(2):150-5.
8. Gaze MN, Kelly CG, Kerr GR, Cull A, Cowie VJ, Gregor A, et al. Pain relief and quality of life following radiotherapy for bone metastases: a randomised trial of two fractionation schedules. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 1997;45(2):109-16.
9. Gutierrez Bayard L, Salas Buzon Mdel C, Angulo Pain E, de Ingunza Baron L. Radiation therapy for the management of painful bone metastases: Results from a randomized trial. Reports of practical oncology and radiotherapy : journal of Greatpoland Cancer Center in Poznan and Polish Society of Radiation Oncology. 2014;19(6):405-11.
10. Hamouda WE, Roshdy W, Teema M. Single versus conventional fractionated radiotherapy in the palliation of painful bone metastases. The Gulf journal of oncology. 2007;1(1):35-41.
11. Hartsell WF, Scott CB, Bruner DW, Scarantino CW, Ivker RA, Roach M, 3rd, et al. Randomized trial of short- versus long-course radiotherapy for palliation of painful bone metastases. Journal of the National Cancer Institute. 2005;97(11):798-804.
12. Kagei K, Suzuki K, Shirato H, Nambu T, Yoshikawa H, Irie G. A randomized trial of single and multifraction radiation therapy for bone metastasis: a preliminary report. Gan no rinsho Japan journal of cancer clinics. 1990;36(15):2553-8.
13. Koswig S, Budach V. [Remineralization and pain relief in bone metastases after after different radiotherapy fractions (10 times 3 Gy vs. 1 time 8 Gy). A prospective study]. Strahlentherapie und Onkologie : Organ der Deutschen Rontgengesellschaft [et al]. 1999;175(10):500-8.
14. Nielsen OS, Bentzen SM, Sandberg E, Gadeberg CC, Timothy AR. Randomized trial of single dose versus fractionated palliative radiotherapy of bone metastases. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 1998;47(3):233-40.
15. Price P, Hoskin PJ, Easton D, Austin D, Palmer SG, Yarnold JR. Prospective randomised trial of single and multifraction radiotherapy schedules in the treatment of painful bony metastases. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 1986;6(4):247-55.
16. Roos DE, Turner SL, O'Brien PC, Smith JG, Spry NA, Burmeister BH, et al. Randomized trial of 8 Gy in 1 versus 20 Gy in 5 fractions of radiotherapy for neuropathic pain due to bone metastases (Trans-Tasman Radiation Oncology Group, TROG 96.05). Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2005;75(1):54-63.
17. Sarkar SK, Sarkar S, Pahari B, et al: Multiple and single fraction palliative radiotherapy in bone secondaries: A prospective study. Ind J Radiol Imag 2002; 12:281-284.
18. van der Linden YM, Lok JJ, Steenland E, Martijn H, van Houwelingen H, Marijnen CA, et al. Single fraction radiotherapy is efficacious: a further analysis of the Dutch Bone Metastasis Study controlling for the influence of retreatment. International journal of radiation oncology, biology, physics. 2004;59(2):528-37.
19. Cole DJ. A randomized trial of a single treatment versus conventional fractionation in the palliative radiotherapy of painful bone metastases. Clinical oncology (Royal College of Radiologists (Great Britain)). 1989;1(2):59-62.
20. Foro P, Algara M, Reig A, Lacruz M, Valls A. Randomized prospective trial comparing three schedules of palliative radiotherapy. Preliminary results. Oncologia. 1998;21(11):55-60.
21. Özsaran Z, Yalman D, Anacak Y, Esassolak M, Haydaroğlu A. Palliative radiotherapy in bone metastases: results of a randomized trial comparing three fractionation schedules. Journal -Balkan Union of Oncology. 2001;6:43-8.
22. Safwat E, El-Nahas T, Metwally H, Abdelmotgally R, Kassem N. Palliative fractionated radiotherapy for bone metastases clinical and biological assessment of single versus multiple fractions. Journal of the Egyptian National Cancer Institute. 2007;19(1):21-7.
23. Meeuse JJ, van der Linden YM, van Tienhoven G, Gans RO, Leer JW, Reyners AK. Efficacy of radiotherapy for painful bone metastases during the last 12 weeks of life: results from the Dutch Bone Metastasis Study. Cancer. 2010;116(11):2716-25.
24. Steenland E, Leer JW, van Houwelingen H, Post WJ, van den Hout WB, Kievit J, et al. The effect of a single fraction compared to multiple fractions on painful bone metastases: a global analysis of the Dutch Bone Metastasis Study. Radiother Oncol. 1999;52(2):101-9. (Same study as reference 18.)

Evidence-to-Decision table 6.1		
In adults (including older persons) and adolescents with pain related to bone metastases, is low-fractionated radiotherapy more effective than high-fractionated radiotherapy for achieving pain control?		
POPULATION:	Adults (including older persons) and adolescents with cancer-related pain	**Background:** Bone pain is the most common type of pain from cancer and is present in approximately one out of three patients with bone metastases.[129,139] The pain is commonly a mixture of background pain and incident/episodic pain, which is commonly associated with weight bearing or movement.[130] Bone metastases can weaken bone sufficiently to greatly increase patients' risk of fracture. Radiotherapy has been shown to reduce pain significantly and is reported to be the most effective treatment specific for cancer-related bone pain. Previous reviews have found no important differences between single dose radiotherapy and multiple dose therapy.[190,191] **Current WHO recommendation**: None
INTERVENTION:	Radiotherapy (low-fractionated)	
COMPARISON:	Radiotherapy (high-fractionated)	
MAIN OUTCOMES:	• Pain relief • Pain relief speed • Pain relief maintenance • Quality of life (QoL) • Functional outcomes • Skeletal-related events • Acute bone flare (adverse event)	
STRATIFICATIONS:	• Age (adults, older persons, adolescents, children) • History of substance abuse • Refractory pain	
SETTING:	All	
PERSPECTIVE:	Population	

	CRITERIA	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** Yes	**Research evidence** None **Additional considerations** Radiotherapy is a relatively expensive therapy limited only to settings with adequate capacity to deliver it. Nevertheless, it is a therapy offered in many countries, including low- and middle-income countries, with well-known therapeutic benefits. WHO guidance is therefore needed on which treatment schedule is preferred: low-fractionated/single dose radiotherapy or high-fractionated/multiple dose radiotherapy?

BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Yes: [ ] No: [ ] Uncertain: [Yes]	• **Twenty-three randomized controlled trials** compared low-fractioned (single dose) radiotherapy to high-fractioned (multiple dose) radiotherapy in patients with a variety of cancer types, with breast, prostate, and lung cancers seen in most studies. Almost all trials used an 8 Gy single dose in the low-fractionated arm; various schedules were used in the high-fractionation arms ranging from from 20 to 30 Gy mostly given over 5 to 10 fractions. Among studies that reported participant ages, study participants were mostly older adults; the mean age ranged from 48 to 72 years old, with the youngest participant being 16 years old. **BENEFITS and HARMS** • **Eighteen trials** provided **high strength of evidence** that the **different fractionation schedules were similarly effective in producing complete pain relief** ("complete response"). Under both schedules, 25% or 26% of participants achieved complete pain relief (RR = 0.97; 95% CI 0.89, 1.06). **Twenty-one trials** provided **high strength of evidence** that the **different fractionation schedules were similarly effective in improving pain relief** ("complete or partial response"). Under both schedules, 69% or 71% of participants achieved either complete or partial pain relief (RR = 0.97; 95% CI 0.93, 0.998). **Three trials** provided **low strength** of evidence of no difference of pain relief (measured on a continuous scale) between fractionation schedules. The difference between groups in pain score on a transformed 0-100 (worst) scale ranged from -5 to 2.5 units. • **Three trials** provided **moderate strength of evidence** of **similar pain relief speed** (time to pain relief) **with both schedules**. No significant differences were found. • **Nine trials** provided **moderate strength of evidence** of **similar pain relief maintenance** (duration of pain relief) **with both schedules**. No significant differences were found. • **Ten trials** provided **high strength of evidence** that rates of **pathological fractures (at the index site)** were **more likely with low-fractionated** compared with high-fractionated radiotherapy (RR = 1.48; 95% CI 1.08, 2.03). • **Three trials** provided **high strength of evidence** that rates of **spinal compression (at the index site)** were **more likely with low-fractionated** compared with high-fractionated radiotherapy (RR = 1.45; 95% CI 0.89, 2.37). • **Three trials** provided **low strength of evidence** of **no significant differences between fractionation schedules in improvements in QoL** (RR = 1.02; 95% CI 0.83, 1.26) measured using various scales. • **Three trials** provided **low strength of evidence** of **no significant differences between fractionation schedules in improvements in physical function** (RR = 1.11; 95% CI 0.84, 1.46) measured using various scales, and **one trial** provided **very low strength of evidence** of **no significant difference between fractionation schedules** in **social function** (RR = 0.98; 95% CI 0.8, 1.20), as measured on the QLQ-C30 scale. • **One trial** provided **low strength of evidence** of **more acute bone flares with low-fractionated** than high-fractionated radiotherapy (RR = 3.45; 95% CI 0.73, 16.3). **STRATIFICATIONS**

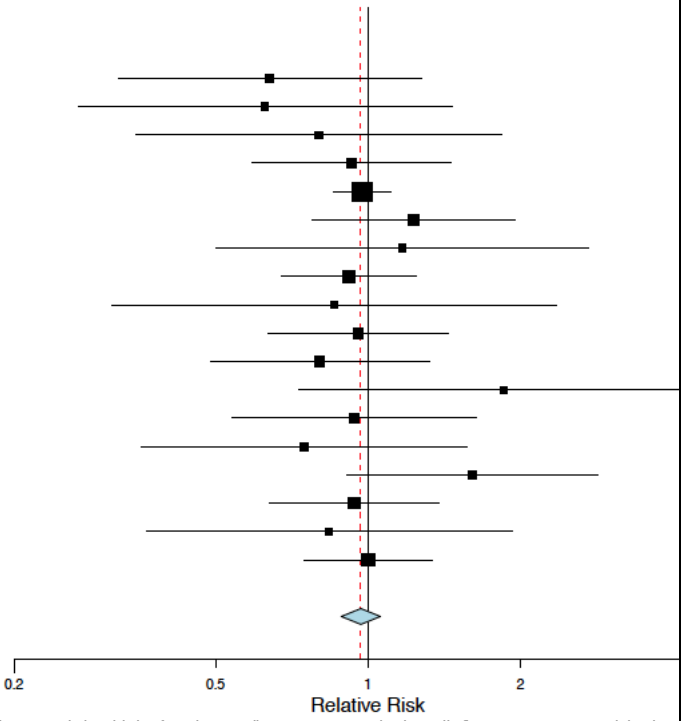
- Studies conducted in adults with a wide age range, without stratification into adolescent, non-older persons, and older persons.
- Studies provide no data regarding history of substance abuse.
- Studies provide no data regarding refractory pain.

SUMMARY

The choice of low-fractionated (single dose) or high-fractionated (multiple dose) radiotherapy makes little or no difference in bone pain relief, but high-fractionated (multiple dose) radiotherapy reduces the risk of pathological fractures and spinal compression at the index sites. The choice of radiotherapy schedule probably makes little or no difference in speed or duration of pain relief and may make little or no difference in quality of life or function. Low-fractionated (single dose) radiotherapy may cause more acute bone flares than high-fractionated (multiple dose) radiotherapy.

Forest Plot 6.1.1. Pain Relief ("Complete Response", Categorical) Single vs. Multiple Fractionated Radiotherapy

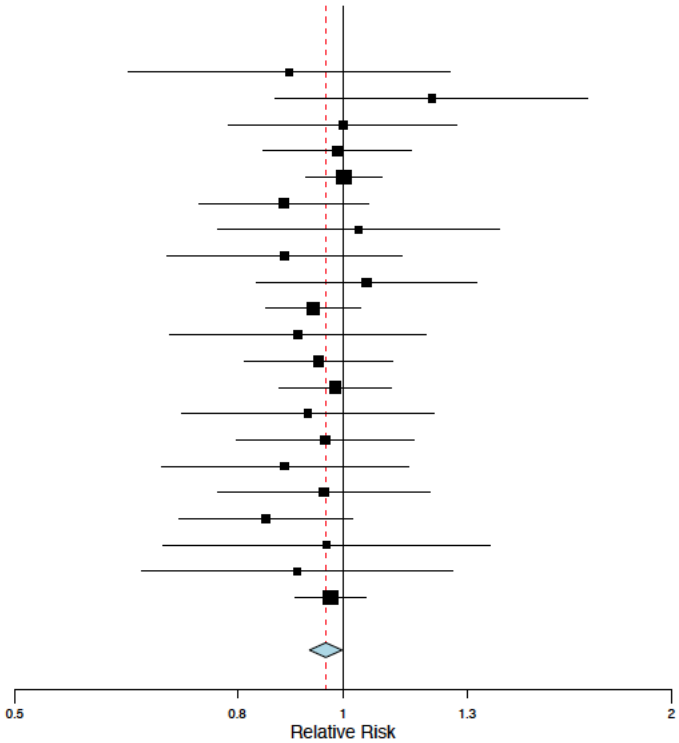
Studies	Estimate (95% CI)	Ev/Trt	Ev/Ctrl
Altundag 2002	0.641 (0.321, 1.276)	7/17	9/14
AmouzegarHashemi 2008	0.626 (0.268, 1.466)	6/27	11/31
Anter 2015	0.800 (0.349, 1.836)	8/44	10/44
Badzio 2003	0.928 (0.590, 1.460)	23/64	24/62
BPTWP 1999	0.974 (0.856, 1.109)	199/351	192/330
Chow 2014	1.230 (0.776, 1.951)	35/258	29/263
Foro Arnalot 2008	1.168 (0.502, 2.721)	10/78	9/82
Gaze 1997	0.915 (0.673, 1.244)	50/129	47/111
Gutierrez Bayard 2014	0.857 (0.312, 2.351)	6/45	7/45
Hamouda 2007	0.957 (0.634, 1.445)	23/50	25/52
Hartsell 2005	0.803 (0.488, 1.321)	25/256	31/255
Kagei 1990	1.857 (0.730, 4.722)	8/14	4/13
Koswig 1999	0.940 (0.539, 1.640)	16/52	18/55
Nielsen 1998	0.749 (0.357, 1.571)	11/106	14/101
Price 1986	1.609 (0.908, 2.850)	22/49	12/43
Roos 2005	0.940 (0.637, 1.385)	35/119	36/115
Sarkar 2002	0.838 (0.365, 1.926)	6/17	8/19
van der Linden 2004	1.002 (0.748, 1.343)	78/556	76/543
Overall (I^2=0 %, P=0.897)	**0.968 (0.886, 1.058)**	**568/2232**	**562/2178**



***Abbreviations**: **BPTWP**: Bone Pain Trial Working Party; **CI**: confidence interval; **Ctrl**: control (multiple fractionated); **Ev**: events (pain relief); **Trt**: treatment (single fractionated).*

Forest Plot 6.1.2. Pain Relief ("Complete or Partial Response", Categorical) Single vs. Multiple Fractionated Radiotherapy

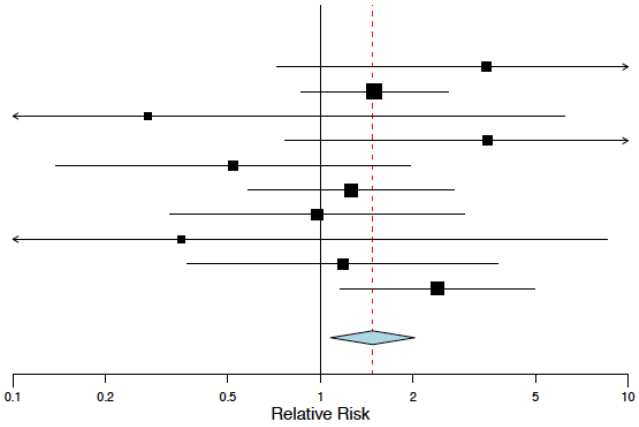
Studies	Estimate (95% CI)	Ev/Trt	Ev/Ctrl
Altundag 2002	0.892 (0.635, 1.253)	13/17	12/14
AmouzegarHashemi 2008	1.206 (0.867, 1.677)	21/27	20/31
Anter 2015	1.000 (0.786, 1.273)	33/44	33/44
Badzio 2003	0.987 (0.845, 1.154)	53/64	52/62
BPTWP 1999	1.002 (0.925, 1.086)	274/351	257/330
Chow 2014	0.882 (0.737, 1.056)	116/258	134/263
Cole 1989	1.034 (0.769, 1.391)	14/16	11/13
Foro 1998	0.884 (0.690, 1.131)	19/25	43/50
Foro Arnalot 2008	1.051 (0.832, 1.328)	51/78	51/82
Gaze 1997	0.939 (0.849, 1.037)	108/129	99/111
Gutierrez Bayard 2014	0.909 (0.693, 1.193)	30/45	33/45
Hamouda 2007	0.950 (0.813, 1.110)	42/50	46/52
Hartsell 2005	0.984 (0.874, 1.109)	187/288	188/285
Kagei 1990	0.929 (0.712, 1.211)	12/14	12/13
Koswig 1999	0.964 (0.799, 1.163)	41/52	45/55
Nielsen 1998	0.885 (0.681, 1.149)	52/106	56/101
Ozsaran 2001	0.961 (0.767, 1.202)	27/36	57/73
Roos 2005	0.850 (0.708, 1.020)	73/119	83/115
Safwat 2007	0.966 (0.684, 1.363)	14/20	29/40
Sarkar 2002	0.908 (0.654, 1.260)	13/17	16/19
van der Linden 2004	0.974 (0.905, 1.049)	395/556	396/543
Overall (I^2=0 %, P=0.989)	**0.965 (0.932, 0.998)**	**1588/2312**	**1673/2341**



Abbreviations: ***BPTWP***: *Bone Pain Trial Working Party;* ***CI***: *confidence interval;* ***Ctrl***: *control (multiple fractionated);* ***Ev***: *events (pain relief);*

Forest Plot 6.1.3. Skeletal Related Events (Pathological Fracture at Index Site) Single vs. Multiple Fractionated Radiotherapy

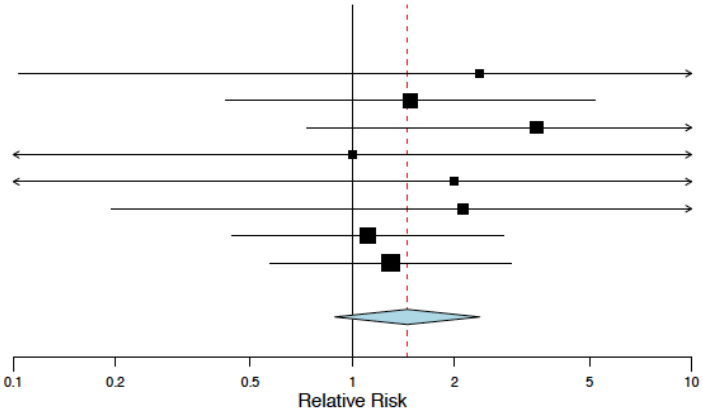
Studies	Estimate (95% CI)	Ev/Trt	Ev/Ctrl
BPTWP 1999	3.454 (0.722, 16.521)	7/383	2/378
Chow 2014	1.500 (0.866, 2.599)	30/425	20/425
Cole 1989	0.275 (0.012, 6.226)	0/16	1/13
Gutierrez Bayard 2014	3.500 (0.768, 15.942)	7/45	2/45
Hamouda 2007	0.520 (0.137, 1.967)	3/50	6/52
Hartsell 2005	1.259 (0.582, 2.727)	14/288	11/285
Nielsen 1998	0.975 (0.324, 2.939)	6/122	6/119
Price 1986	0.352 (0.014, 8.575)	0/140	1/148
Roos 2005	1.182 (0.370, 3.783)	6/137	5/135
van der Linden 2004	2.396 (1.156, 4.965)	24/579	10/578
Overall (I^2=0 % , P=0.421)	**1.478 (1.078, 2.027)**	**97/2185**	**64/2178**



Abbreviations: ***BPTWP***: *Bone Pain Trial Working Party;* ***CI***: *confidence interval;* ***Ctrl***: *control (multiple fractionated);* ***Ev***: *events (skeletal related event);* ***Trt***: *treatment (single fractionated).*

Forest Plot 6.1.4. Skeletal Related Events (Spinal Cord Compression at Index Site) Single vs. Multiple Fractionated Radiotherapy

Studies	Estimate (95% CI)	Ev/Trt	Ev/Ctrl
Altundag 2002	2.368 (0.104, 54.078)	1/18	0/14
BPTWP 1999	1.480 (0.421, 5.204)	6/383	4/378
Chow 2014	3.500 (0.731, 16.751)	7/425	2/425
Gutierrez Bayard 2014	1.000 (0.020, 49.332)	0/45	0/45
Ozsaran 2001	2.000 (0.040, 98.806)	0/36	0/73
Price 1986	2.114 (0.194, 23.058)	2/140	1/148
Roos 2005	1.109 (0.441, 2.788)	9/137	8/135
van der Linden 2004	1.298 (0.574, 2.936)	13/579	10/578
Overall (I^2=0 % , P=0.967)	**1.451 (0.887, 2.374)**	**38/1763**	**25/1796**



Abbreviations: ***BPTWP***: *Bone Pain Trial Working Party;* ***CI***: *confidence interval;* ***Ctrl***: *control (multiple fractionated);* ***Ev***: *events (skeletal related event);* ***Trt***: *treatment (single fractionated).*

ACCEPTABILITY & PREFERENCES	**Is there important uncertainty or variability about how much people value the options?** Major variability ☐ Minor variability ☒ Yes Uncertain ☐ **Is the option acceptable to key stakeholders?** Yes ☒ Yes ☐ No ☐ Uncertain	**<u>Research evidence</u>** Single dose radiotherapy, where a patient receives a larger single dose (e.g. a 8Gy fraction) in a single clinic visit, is less expensive in terms of both time and money than a longer schedule where a patient receives smaller individual doses but an overall greater amount of radiotherapy split over several visits (e.g. 20-30 Gy given over 5-10 fractions)[192]. Prices vary widely due to global variation in the price of services. With negligble clinical differences, patients would probably prefer single dose therapy. **<u>Additional considerations</u>** Private clinics may prefer to deliver multiple dose radiotherapy as it delivers greater profits, but, overall, key stakeholders accept the option.

FEASIBILITY ./ RESOURCE USE

How large are the resource requirements?

Major	Minor	Uncertai
Yes		

	Price (USD) from studies cited in [192]		
	Median	Minimum	Maximum
Single dose	$ 998	$ 222	$ 2438
Multiple dose	$ 2316	$ 724	$ 3311

Is the option feasible to implement?

Yes	No	Uncertain
Yes		

If more patients were to be given single dose therapy, in settings where there is a shortage of radiation equipment and staff, the same resources could be used for greater coverage, as well as having lower costs to patients such as travel, making the single dose option the most feasible.

Would the option improve equity in health?

Yes	No	Uncertai
Yes		

Research evidence

None

Additional considerations

As for resource and feasibility considerations above, if more patients were to be given single dose therapy, in settings where there is a shortage of radiation equipment and staff, the same resources could be used for greater coverage, as well as having lower costs to patients such as travel, making the single dose option the most feasible

Recommendation	**Current recommendation:** None. **New (draft) recommendation:** In adults (including older persons) and adolescents with pain related to bone metastases, single-fraction (single dose) radiotherapy should be used when radiotherapy is indicated.
Strength of Recommendation	**Strong**
Quality of Evidence	➢ **HIGH/MODERATE** [Pain relief (critical) = high (categorical), low (continuous) Pain relief speed (critical) = moderate Pain relief maintenance (critical) = moderate Skeletal-related events, pathological fracture (important) = high Skeletal-related events, spinal cord compression (important) = high QoL (important) = low Functional outcomes (important) = low Acute bone flare (important) = low]
Justification	The choice of low-fractionated (single dose) or high-fractionated (multiple dose) radiotherapy makes little or no difference in bone pain relief, but high-fractionated (multiple dose) radiotherapy reduces the risk of pathological fractures and spinal compression at the index sites. The choice of radiotherapy schedule probably makes little or no difference in speed or duration of pain relief. The choice of radiotherapy schedule may make little or no differnce in quality of life or functional status. Low-fractionated (single dose) radiotherapy may cause more acute bone flares than high-fractionated (multiple dose) radiotherapy. Therefore the negligible clinical differences between the schedules and the large cost and equity benefits possible, single dose should be used in favour of multiple dose radiotherapy where indicated. This means it should be used for people already with painful metastases, not for their prevention.
Subgroup considerations	

Implementation considerations [incl. M&E]
Research priorities

6.2. In adults (including older persons) and adolescents with pain related to bone metastases, what is the evidence for radiotherapy or radioisotopes as compared with no radiotherapy or radioisotopes in order to achieve rapid, effective, and safe pain control?

Nine RCTs compared radioisotopes to a control arm that did not use radioisotopes.[193-201] In one trial, the radioisotopes were used as adjuvants to external beam radiotherapy.[198] Almost all trial participants were men with prostate cancer. The studies evaluated strontium-89 (3 trials), samarium-153 (3 trials), rhenium-186 (2 trials), and radium-223 (1 trial). Study participants were mostly older adults; the mean age ranged from 63 to 71 years.

Evidence Table 6.2 summarizes the findings from the RCTs (citations are provided in the table). Five trials provided moderate strength of evidence of net improvement in pain with radioisotopes compared with placebo. The magnitude of the difference in VAS scores (on a transformed 0 to 100 scale) varied from 6.5 to 75 units, but all trials found better pain scores after radioisotope treatment, with an average 41 (95% CI 18, 64) unit net improvement. Two trials provided very low quality of evidence that complete pain relief is statistically significantly more likely after radioisotopes (RR 1.92; 95% CI 1.18, 3.12) and four trials provided very low quality of evidence of more likely complete or partial pain relief with radioisotopes (RR 1.35; 95% CI 0.89, 2.07), but this was not statistically significant. No study reported pain relief speed or pain reduction maintenance.

Two studies provided high quality evidence that skeletal-related events were less common after radiotherapy than placebo (RR = 0.86; 95% CI 0.77, 0.95) and that skeletal-related events were delayed among those who had received radiotherapy compared with placebo (HR = 0.73; 95% CI 0.62, 0.86). The two studies provided low quality evidence of similar risk of fracture (RR = 1.05; 95% CI 0.53, 2.08) and spinal cord compression (RR = 0.82; 95% CI 0.39, 1.71). One of the trials provided very low quality evidence of no difference for bone surgery (RR = 1.46; 95% CI 0.69, 3.10) and low quality evidence for no difference in hypercalcemia (RR = 5.01, 95% CI 0.24, 104).

Two studies provided moderate strength of evidence that quality of life was improved more with radiotherapy than placebo. This outcome was measured both categorically in one study (RR = 1.57; 95% CI 1.17, 2.10; providing low strength of evidence) and continuously in two studies (difference = 1.5; 95% CI -0.4, 3.3 on a transformed 0 to 100 [best] scale; moderate strength of evidence). One study provided very low strength of evidence of no difference in functional outcomes (social or physical) with radiotherapy or placebo. However, while the study reported that there were no significant difference in effects, the data provided suggested a statistically significant difference in social function favouring placebo (between-group difference -1.1; 95% CI -1.9, -0.3) and a significant difference in physical function favouring radiotherapy (between arm difference 1.4; 95% CI 0.5, 2.3). Three trials provided low strength of evidence of no difference in occurrences of bone flares with radiotherapy (RR =1.30; 95% CI 0.50, 3.42).

Evidence Profile 6.2. Radiotherapy vs. Placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Radiotherapy**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Bone pain relief (categorical) (complete response, follow up: 1-3 months; assessed with: VAS<15 or "pain free")												
2 [1,2]	RCT	serious [A]	not serious	serious [B]	none	none	51/134 (38%)	17/85 (20%)	**RR 1.92** (1.18, 3.12)	**351 more per 1000** (from 69 to 807 more)	Low	CRITICAL
Bone pain relief (categorical) (improvement [complete or partial response], follow up: 2-3 months or nd; assessed with: VAS≥2/10 reduction in bone pain ["very good"])												
4 [1,3,4,5]	RCT	very serious [D]	not serious	not serious	serious [C]	none	71/107 (66%)	45/104 (43%)	**RR 1.35** (0.89, 2.07)	**235 more per 1000** (from 75 fewer to 707 more)	Very Low	CRITICAL
Pain relief (continuous) (follow up: range 1 to 2 months; assessed with: VAS, NRS; Scale: 0 to 100 [worst] [E])												
5 [2,4,5,6,8]	RCT	serious [F]	not serious [G]	not serious	not serious	none	241	145	**Diff -41** (-64, -18)		Moderate	CRITICAL
Pain reduction maintenance												
0									not estimable			CRITICAL
Skeletal-related events, any (follow up: range 1.8 to 3 years)												
2 [8,9]	RCT	not serious	not serious	not serious	not serious	none	427/978 (43%)	345/680 (50%)	**RR 0.86** (0.77, 0.95) HR 0.73 (0.62, 0.86) [H]	**34 fewer per 1000** (from 20 to 83 fewer)	High	IMPORTANT
Skeletal-related events, fracture (follow up: range 1.8 to 3 years)												
2 [8,9]	RCT	not serious	serious [I]	not serious	serious [J]	none	47/978 (4.8%)	32/680 (5.1%)	RR 1.05 (0.53, 2.08)	**3 fewer per 1000** (from 55 fewer to 24 more)	Low	
Skeletal-related events, spinal cord compression (follow up: range 1.8 to 3 years)												
2 [8,9]	RCT	not serious	serious [I]	not serious	serious [J]	none	76/978 (8.3%)	67/680 (9.7%)	RR 0.82 (0.39, 1.71)	**18 fewer per 1000** (from 59 fewer to 69 more)	Low	
Skeletal-related events, bone surgery (follow up: 1.8 years)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radiotherapy	Placebo	Relative (95% CI)	Absolute (95% CI)		
1 [8]	RCT	not serious	N/A	not serious	serious [J]	single study	16/378 (4.2%)	11/379 (2.9%)	RR 1.46 (0.69, 3.10)	**13 more per 1000** (from 13 fewer to 40 more)	Low	
Skeletal-related events, hypercalcemia (follow up: 1.8 years)												
1 [8]	RCT	not serious	N/A	not serious	very serious [J]	single study	2/378 (0.5%)	0/379 (0%)	RR 5.01 (0.24, 104)	**5 more per 1000** (from 2 fewer to 13 more)	Very Low	
Quality of life (categorical) (follow up: 3 years; assessed with: FACT-P; improvement ≥10 increase on a scale of 0 to 156 [best])												
1 [9]	RCT	not serious	not serious	serious [K]	not serious	single study	150/600 (25%)	48/301 (16%)	**RR 1.57** (1.17, 2.10)	90 more per 1000 (from 27 to 176 more)	Low	IMPORTANT
Quality of life (follow up: range 1.8 to 3 years; assessed with: FACT-P; Scale: 0 to 100 [best] [E])												
2 [8,9]	RCT	not serious	not serious	serious [K]	not serious	none	3427	3047	Diff 1.5 (-0.4, 3.3)		Moderate	IMPORTANT
Functional outcomes, Social (follow up: 1.8 years; assessed with: FACT-P-social; Scale: 0 to 100 [best] [E])												
1 [8]	RCT	not serious	not serious	serious [K]	serious [J]	single study	2993	2921	Diff -1.1 (-1.9, -0.3) [L]		Very Low	IMPORTANT
Functional outcomes, Physical (follow up: 1.8 years; assessed with: FACT-P-physical; Scale: 0 to 100 [best] [E])												
1 [8]	RCT	not serious	not serious	serious [H]	serious [I]	single study	2993	2921	Diff 1.4 (0.5, 2.3) [L]		Very Low	IMPORTANT
Adverse events: bone flare (follow up: soon after treatment)												
3 [2,5,7]	RCT	not serious	not serious	not serious	very serious [C, J]	none	13/192 (6.8%)	5/102 (4.9%)	**RR 1.30** (0.50, 3.42)	20 more per 1000 (from 34 fewer to 164 more)	Low	IMPORTANT

***Abbreviations: CI**: confidence interval; **Diff**: difference (between groups); **FACT**: Functional Assessment of Cancer Therapy; **HR**: hazard ratio; **nd**: no data (not reported); **NS:** not statistically significant**; RCT**: randomized controlled trial(s); **RR**: relative risk (log scale); **VAS**: Visual Analog Scale.*

Explanations

A. High attrition rate.
B. One trial's outcome was not true complete response (VAS <15); other trial did not define pain free.
C. Fewer than 300 participants.
D. High attrition rate, lack of blinding, possible selective outcome reporting, no data on follow up time.
E. Scales transformed to 0 to 100, as necessary.
F. High attrition rate, lack of blinding, possible selective outcome reporting.
G. Inconsistent in magnitude but not in direction. See figure.
H. Reported in Radiotherapy 13.6 and 15.6 months until first skeletal-related event. Placebo 11.2 and 9.8 months, respectively.
I. The two study estimates were in opposite directions.
J. Wide confidence interval.
K. FACT (total score) is a measure of quality of life that mix concepts of both quality of life and functional outcomes. We treated the total score as a quality of life measure and the relevant subscores as functional outcomes, but these do not cleanly measure function.
L. Not statistically significant per study (therefore the calculated estimate here from the single study is inaccurately precise).

References

1. Porter AT, McEwan AJ. Strontium-89 as an adjuvant to external beam radiation improves pain relief and delays disease progression in advanced prostate cancer: results of a randomized controlled trial. Seminars in oncology. 1993;20(3 Suppl 2):38-43.
2. Sartor O, Reid RH, Hoskin PJ, Quick DP, Ell PJ, Coleman RE, et al. Samarium-153-Lexidronam complex for treatment of painful bone metastases in hormone-refractory prostate cancer. Urology. 2004;63(5):940-5.
3. Buchali K, Correns HJ, Schuerer M, Schnorr D, Lips H, Sydow K. Results of a double blind study of 89-strontium therapy of skeletal metastases of prostatic carcinoma. European journal of nuclear medicine. 1988;14(7-8):349-51.
4. Han SH, de Klerk JM, Tan S, van het Schip AD, Derksen BH, van Dijk A, et al. The PLACORHEN study: a double-blind, placebo-controlled, randomized radionuclide study with (186)Re-etidronate in hormone-resistant prostate cancer patients with painful bone metastases. Placebo Controlled Rhenium Study. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2002;43(9):1150-6.
5. Storto G, Gallicchio R, Pellegrino T, Nardelli A, De Luca S, Capacchione D, et al. Impact of (1)(8)F-fluoride PET-CT on implementing early treatment of painful bone metastases with Sm-153 EDTMP. Nuclear medicine and biology. 2013;40(4):518-23.
6. Maxon HR, 3rd, Schroder LE, Hertzberg VS, Thomas SR, Englaro EE, Samaratunga R, et al. Rhenium-186(Sn)HEDP for treatment of painful osseous metastases: results of a double-blind crossover comparison with placebo. Journal of nuclear medicine. 1991;32(10):1877-81.
7. Serafini AN, Houston SJ, Resche I, Quick DP, Grund FM, Ell PJ, et al. Palliation of pain associated with metastatic bone cancer using samarium-153 lexidronam: a double-blind placebo-controlled clinical trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 1998;16(4):1574-81.
8. James N, Pirrie S, Pope A, Barton D, Andronis L, Goranitis I, et al. TRAPEZE: a randomised controlled trial of the clinical effectiveness and cost-effectiveness of chemotherapy with zoledronic acid, strontium-89, or both, in men with bony metastatic castration-refractory prostate cancer. Health technology assessment (Winchester, England). 2016;20(53):1-288.
9. Parker C, Nilsson S, Heinrich D, Helle SI, O'Sullivan JM, Fossa SD, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. The New England journal of medicine. 2013;369(3):213-23.

Evidence-to-Decision table 6.2		
In adults (including older persons) and adolescents with pain related to bone metastases, is radiotherapy more effective than no radiotherapy for achieving pain control?		
POPULATION:	Adults (including older persons) and adolescents with cancer-related pain	**Background:** Bone pain is the most common type of pain from cancer and is present in approximately one out of three patients with bone metastases.[129,139] The pain is commonly a mixture of background pain and incident/episodic pain, which is commonly associated with weight bearing or movement.[130] Bone metastases can weaken bone sufficiently to greatly increase patients' risk of fracture. Radioisotopes can be administered for diffuse bone pain that is ineligible for radiotherapy. **Current WHO recommendation**: None
INTERVENTION:	Radioisotopes or radiotherapy	
COMPARISON:	Placebo (no treatment)	
MAIN OUTCOMES:	• Bone pain relief • Pain relief maintenance • Quality of life (QoL) • Functional outcomes • Skeletal-related events • Bone pain (adverse event)	
STRATIFICATIONS:	• Age (adults, older persons, adolescents, children) • History of substance abuse • Refractory pain	
SETTING:	All	
PERSPECTIVE:	Population	

	CRITERIA	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** None	**Research evidence** None **Additional considerations** Due to the high cost of treatment worldwide calling into question the global relevancy of the therapy, as well as the homogeneity of evidence, the GDG did not feel confident issuing a recommendation.

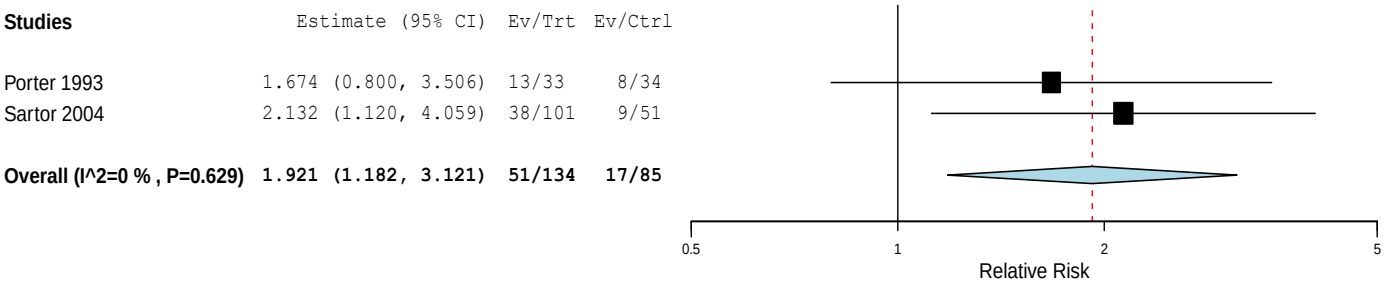
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Yes ☐ No ☐ Uncertain ☒ Yes	• **Nine randomized controlled trials** compared radioisotopes to a control with no radioisotopes in patients almost all with prostate cancer. The studies evaluated strontium-89 (3 trials), samarium-153 (3 trials), rhenium-186 (2 trials), and radium-223 (1 trial). Trials were mostly conducted in older adults. **BENEFITS and HARMS** • **Five trials** provided **moderate strength of evidence** of **better bone pain relief with radioisotope treatment**. The net difference in bone pain was -41 points (on a 0 to 100 [worst] scale; 95% CI -64, -18), favouring radioisotopes. **Two and four trials**, respectively, provided **very low strength of evidence** that **bone pain relief** was **more common after radioisotopes** (38%) versus placebo (20%, RR = 1.92; 95% CI 1.18, 3.12) and that **bone pain improvement** was **more common after radioisotopes** (66%) versus placebo (43%, RR = 1.35; 95% CI 0.89, 2.07) . • **No trial** reported on **pain relief speed**. • **No trial** reported on **pain relief maintenance**. • **Two trials** provided **high strength of evidence** that **skeletal related events (any) were less common after radioisotopes than placebo** (RR = 0.86; 95% CI 0.77, 0.95) and that **skeletal related events were delayed among those who had received radioisotopes compared to placebo** (HR = 0.73; 95% CI 0.62, 0.86). • **Two trials** provided **low strength of evidence** of **similar risk of fracture** (RR = 1.05; 95% CI 0.53, 2.08) • **Two trials** provided **low strength of evidence** of **similar risk of spinal cord compression** (RR = 0.82; 95% CI 0.39, 1.71). • **One trial** provided **very low strength of evidence** for **bone surgery** (RR = 1.46; 95% CI 0.69, 3.10). • **One trial** provided **very low strength of evidence** for **hypercalcemia** (RR = 5.01, 95% CI 0.24, 104). • **Two trials** provided **moderate strength of evidence** that **QoL was probably improved more with radioisotopes than placebo** when measured continuously (difference = 1.5; 95% CI -0.4, 3.3 on a transformed 0 to 100 [best] scale). **One trial** provided **low strength of evidence** that **QoL may be improved more with radioisotopes than placebo** when measured categorically (RR = 1.57; 95% CI 1.17, 2.10). • **One trial** provided **very low strength of evidence** regarding **functional outcomes (social or physical) with radioisotopes or placebo**: social function favoring placebo (between-group difference -1.1; 95% CI -1.9, -0.3), physical function favoring radioisotopes (between arm difference 1.4; 95% CI 0.5, 2.3); both not statistically significant per trial authors. • **Three trials** provided **low strength of evidence** of **no difference in episodes of acute bone flares with radioisotopes** (6.8%, RR = 1.30; 95% CI 0.50, 3.42) than placebo (4.9%). **STRATIFICATIONS** • Studies conducted in mostly older adults with a mostly narrow age range, without stratification into adolescent, non-older persons, and older persons. • Studies provide no data regarding history of substance abuse.

- Studies provide no data regarading refractory pain.

SUMMARY

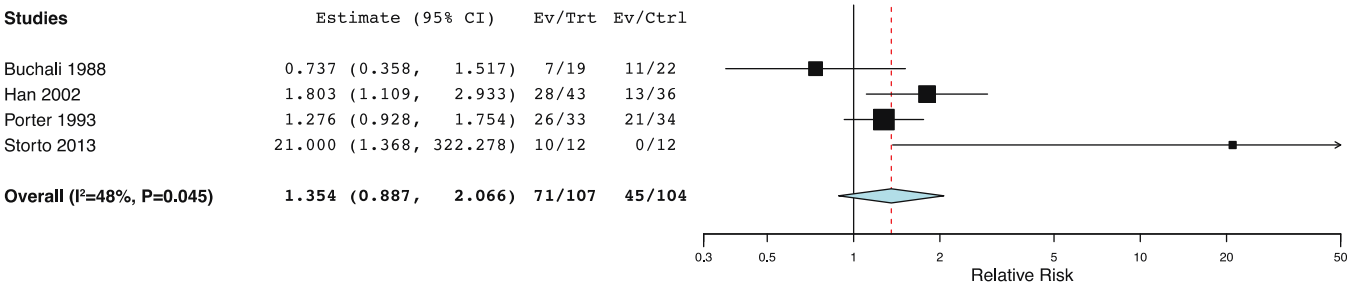
Radioisotope treatment reduces and delays skeletal related events, probably reduces bone pain and improves QoL.

Forest Plot 6.2.1. Pain Relief ("Complete Response", Categorical) Radioisotope Versus Placebo



***Abbreviations**: **CI**: confidence interval; **Ctrl**: control (radioisotope); **Ev**: events (pain relief); **Trt**: treatment (placebo).*

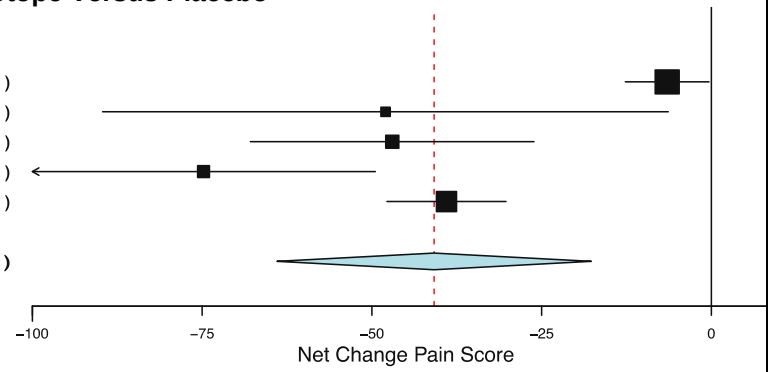
Forest Plot 6.2.2. Pain Improvement ("Complete or Partial Response", Categorical) Radioisotope Versus Placebo



***Abbreviations**: **CI**: confidence interval; **Ctrl**: control (radioisotope); **Ev**: events (pain relief); **Trt**: treatment (placebo).*

Forest Plot 6.2.3. Pain Relief (Continuous) Radioisotope Versus Placebo

Studies	Estimate (95% CI)
Han 2002	−6.500 (−12.672, −0.328)
Maxon 1991	−48.000 (−89.661, −6.339)
Sartor 2004	−47.000 (−67.886, −26.114)
Serafini 1998	−74.785 (−100.068, −49.502)
Storto 2013	−39.000 (−47.765, −30.235)
Overall (I^2=93%, P< 0.001)	**−40.826 (−63.976, −17.675)**

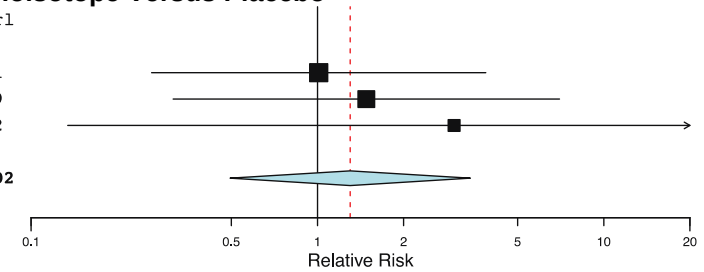


Abbreviation: ***CI***: *confidence interval.*

Scores from individual studies have been transformed to a uniform 0-100 scale (100 = worst).

Forest Plot 6.2.4. Bone Flares (Adverse Event) Radioisotope Versus Placebo

Studies	Estimate (95% CI)	Ev/Trt	Ev/Ctrl
Sartor 2004	1.010 (0.263, 3.874)	6/101	3/51
Serafini 1998	1.481 (0.313, 7.003)	6/79	2/39
Storto 2013	3.000 (0.134, 67.056)	1/12	0/12
Overall (I^2=0%, P=0.802)	**1.301 (0.495, 3.419)**	**13/192**	**5/102**



Abbreviations: ***CI***: *confidence interval;* ***Ctrl***: *control (radioisotope);* ***Ev***: *events (pain relief);* ***Trt***: *treatment (placebo).*

ACCEPTABILITY & PREFERENCES	**Is there important uncertainty or variability about how much people value the options?** Major variability [ ] Minor variability [ ] Uncertain [Yes] **Is the option acceptable to key stakeholders?** Yes [ ] No [ ] Uncertain [Yes]	**<u>Research evidence</u>** None **<u>Additional considerations</u>** None

FEASIBILITY ./ RESOURCE USE	**How large are the resource requirements?** Major ☐ Minor ☐ Uncertai Yes **Is the option feasible to implement?** Yes ☐ No ☐ Uncertain Yes	**Research evidence** None **Additional considerations** None
	Would the option improve equity in health? Yes ☐ No ☐ Uncerta Yes	**Research evidence** None **Additional considerations** None

Recommendation	**Current recommendation:** None **New (draft) recommendation:** None
Strength of Recommendation	
Quality of Evidence	➢ **LOW** [Bone pain (critical) = very low (categorical), moderate (continuous) Any SRE (important) = high QoL (important) = low (categorical), moderate (continuous) Acute bone flare (important) = low other outcomes omitted for no data, conflicting, no difference, or indeterminate findings]
Justification	Radioisotopes are not a priority for WHO to make guidance due to price and homogeneity of evidence.
Subgroup considerations	
Implementation considerations [incl. M&E]	
Research priorities	

References

1. Riley, J*., et al.* Morphine or oxycodone for cancer-related pain? A randomized, open-label, controlled trial. *J Pain Symptom Manage* **49**, 161-172 (2015).
2. Corli, O., Floriani, I., Roberto, A. & al., e. Are strong opioids equally effective and safe in the treatment of chronic cancer pain? A multicenter randomized phase IV 'real life' trial on the variability of response to opioids. *Annals of oncology : official journal of the European Society for Medical Oncology* **27**, 1107-1115 (2016).
3. Zecca, E*., et al.* Comparison of the Tolerability Profile of Controlled-Release Oral Morphine and Oxycodone for Cancer Pain Treatment. An Open-Label Randomized Controlled Trial. *J Pain Symptom Manage* **52**, 783-794 e786 (2016).
4. Bandieri, E*., et al.* Randomized Trial of Low-Dose Morphine Versus Weak Opioids in Moderate Cancer Pain. *J Clin Oncol* **34**, 436-442 (2016).
5. Strobel, E. [Drug therapy in severe tumor pain. Comparative study of a new combination preparation versus diclofenac-Na]. *Fortschr Med* **110**, 411-414 (1992).
6. Knaul, F.M*., et al.* Alleviating the access abyss in palliative care and pain relief-an imperative of universal health coverage: the Lancet Commission report. *Lancet*, Online (2017).
7. World Health Organization. Cancer Factsheet. (2017).
8. van den Beuken-van Everdingen, M.H., Hochstenbach, L.M., Joosten, E.A., Tjan-Heijnen, V.C. & Janssen, D.J. Update on Prevalence of Pain in Patients With Cancer: Systematic Review and Meta-Analysis. *J Pain Symptom Manage* **51**, 1070-1090 e1079 (2016).
9. Krakauer, E.L., Wenk, R., Buitrago, R., Jenkins, P. & Scholten, W. Opioid inaccessibility and its human consequences: reports from the field. *J Pain Palliat Care Pharmacother* **24**, 239-243 (2010).
10. Berterame, S*., et al.* Use of and barriers to access to opioid analgesics: a worldwide, regional, and national study. *The Lancet* **387**, 1644-1656 (2016).
11. MD Magazine. Why are we still talking about opiophobia? (2011).
12. Pastrana, T., Wenk, R., Radbruch, L., Ahmed, E. & De Lima, L. Pain Treatment Continues To Be Inaccessible for Many Patients Around the Globe: Second Phase of Opioid Price Watch, a Cross-Sectional Study To Monitor the Prices of Opioids. *Journal of Palliative Medicine*, 20(24): 378-387 (2017).
13. World Health Organization. Ensuring balance in national policies on controlled substances: Guidance for availability and accessibility of controlled medicines. (2011).
14. Ahmedzai, S. & Brooks, D. Transdermal fentanyl versus sustained-release oral morphine in cancer pain: preference, efficacy, and quality of life. The TTS-Fentanyl Comparative Trial Group. *J Pain Symptom Manage* **13**, 254-261 (1997).
15. Arkinstall, W.W., Goughnour, B.R., White, J.A. & Stewart, J.H. Control of severe pain with sustained-release morphine tablets v. oral morphine solution. *CMAJ* **140**, 653-657, 661 (1989).
16. Beaver, W.T., Wallenstein, S.L., Houde, R.W. & Rogers, A. A clinical comparison of the analgesic effects of methadone and morphine administered intramuscularly, and of orally and parenterally administered methadone. *Clin Pharmacol Ther* **8**, 415-426 (1967).
17. Broomhead, A*., et al.* Comparison of a once-a-day sustained-release morphine formulation with standard oral morphine treatment for cancer pain. *J Pain Symptom Manage* **14**, 63-73 (1997).
18. Bruera, E*., et al.* Randomized, double-blind, cross-over trial comparing safety and efficacy of oral controlled-release oxycodone with controlled-release morphine in patients with cancer pain. *J Clin Oncol* **16**, 3222-3229 (1998).
19. Chen YZ, W., Liang, H. & Wu, G. The analgesic effect of ibuprofen-codeine sustained release tablets on postoperative and cancer pain. *Chinese Journal of Clinical Rehabilitation* **7**, 1290-1291 (2003).

20. Finn, J.*, et al.* Placebo-blinded study of morphine sulfate sustained-release tablets and immediate-release morphine sulfate solution in outpatients with chronic pain due to advanced cancer. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology* **11**, 967-972 (1993).
21. Gabrail, N.Y., Dvergsten, C. & Ahdieh, H. Establishing the dosage equivalency of oxymorphone extended release and oxycodone controlled release in patients with cancer pain: a randomized controlled study. *Curr Med Res Opin* **20**, 911-918 (2004).
22. Hagen, N.A. & Babul, N. Comparative clinical efficacy and safety of a novel controlled-release oxycodone formulation and controlled-release hydromorphone in the treatment of cancer pain. *Cancer* **79**, 1428-1437 (1997).
23. Hanna, M., Thipphawong, J. & Study, G. A randomized, double-blind comparison of OROS(R) hydromorphone and controlled-release morphine for the control of chronic cancer pain. *BMC Palliat Care* **7**, 17 (2008).
24. Heiskanen, T. & Kalso, E. Controlled-release oxycodone and morphine in cancer related pain. *Pain* **73**, 37-45 (1997).
25. Homsi, J.*, et al.* A comparative study of 2 sustained-release morphine preparations for pain in advanced cancer. *Am J Hosp Palliat Care* **27**, 99-105 (2010).
26. Kalso, E. & Vainio, A. Morphine and oxycodone hydrochloride in the management of cancer pain. *Clin Pharmacol Ther* **47**, 639-646 (1990).
27. Klepstad, P., Kaasa, S., Jystad, A., Hval, B. & Borchgrevink, P.C. Immediate- or sustained-release morphine for dose finding during start of morphine to cancer patients: a randomized, double-blind trial. *Pain* **101**, 193-198 (2003).
28. Koch, A.*, et al.* Effect of celecoxib on survival in patients with advanced non-small cell lung cancer: a double blind randomised clinical phase III trial (CYCLUS study) by the Swedish Lung Cancer Study Group. *Eur J Cancer* **47**, 1546-1555 (2011).
29. Kress, H.G.*, et al.* Direct conversion from tramadol to tapentadol prolonged release for moderate to severe, chronic malignant tumour-related pain. *Eur J Pain* **20**, 1513-1518 (2016).
30. Marinangeli, F.*, et al.* Improved cancer pain treatment using combined fentanyl-TTS and tramadol. *Pain practice : the official journal of World Institute of Pain* **7**, 307-312 (2007).
31. Mercadante, S.*, et al.* Morphine versus methadone in the pain treatment of advanced-cancer patients followed up at home. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **16**, 3656-3661 (1998).
32. Minotti, V.*, et al.* A double-blind study comparing two single-dose regimens of ketorolac with diclofenac in pain due to cancer. *Pharmacotherapy* **18**, 594-508 (1998).
33. Mucci-LoRusso, P.*, et al.* Controlled-release oxycodone compared with controlled-release morphine in the treatment of cancer pain: a randomized, double-blind, parallel-group study. *Eur J Pain* **2**, 239-249 (1998).
34. Pannuti, F., Robustelli della Cuna, G., Ventaffrida, V., Strocchi, E. & Camaggi, C.M. A double-blind evaluation of the analgesic efficacy and toxicity of oral ketorolac and diclofenac in cancer pain. The TD/10 recordati Protocol Study Group. *Tumori* **85**, 96-100 (1999).
35. Poulain, P. A study to evaluate the effectiveness and safety of CG5503 (tapentadol) in the treatment of chronic tumor-related pain compared with placebo and morphine. *ClinicalTrialsgov*, NCT00505414 (2010).
36. Rodríguez, M.*, et al.* Double-blind evaluation of short-term analgesic efficacy of orally administered dexketoprofen trometamol and ketorolac in bone cancer pain. *Pain* **104**, 103-110 (2003).
37. Ventafridda, V., Ripamonti, C., Bianchi, M., Sbanotto, A. & De Conno, F. A randomized study on oral administration of morphine and methadone in the treatment of cancer pain. *J Pain Symptom Manage* **1**, 203-207 (1986).

38. Walsh, T.D.*, et al.* A controlled study of sustained-release morphine sulfate tablets in chronic pain from advanced cancer. *Am J Clin Oncol* **15**, 268-272 (1992).
39. Wilder-Smith, C.H., Schimke, J., Osterwalder, B. & Senn, H.J. Oral tramadol, a mu-opioid agonist and monoamine reuptake-blocker, and morphine for strong cancer-related pain. *Ann Oncol* **5**, 141-146 (1994).
40. Wong, J.O., Chiu, G.L., Tsao, C.J. & Chang, C.L. Comparison of oral controlled-release morphine with transdermal fentanyl in terminal cancer pain. *Acta Anaesthesiol Sin* **35**, 25-32 (1997).
41. Rodriguez, M.*, et al.* Efficacy and tolerance of oral dipyrone versus oral morphine for cancer pain. *Eur J Cancer* **30a**, 584-587 (1994).
42. Sittl, R., Griessinger, N. & Likar, R. Analgesic efficacy and tolerability of transdermal buprenorphine in patients with inadequately controlled chronic pain related to cancer and other disorders: a multicenter, randomized, double-blind, placebo-controlled trial. *Clinical therapeutics* **25**, 150-168 (2003).
43. Staquet, M., Gantt, C. & Machin, D. Effect of a nitrogen analog of tetrahydrocannabinol on cancer pain. *Clin Pharmacol Ther* **23**, 397-401 (1978).
44. Staquet, M., Luyckx, A. & Van Cauwenberge, H. A double-blind comparison of alclofenac, pentazocine, and codeine with placebo control in pathologic pain. *The Journal of clinical pharmacology and new drugs* **11**, 450-455 (1971).
45. Staquet, M. & Renaud, A. Double-blind, randomized trial of piroxicam and codeine in cancer pain. *Current Therapeutic Research* **53**, 435-440 (1993).
46. Minotti, V.*, et al.* Double-blind evaluation of short-term analgesic efficacy of orally administered diclofenac, diclofenac plus codeine, and diclofenac plus imipramine in chronic cancer pain. *Pain* **74**, 133-137 (1998).
47. Bauer, M., Schmid, H. & Schulz-Wentland, R. Gynecologic carcinoma patients with chronic pain. Comparison of sublingual buprenorphine with tilidine plus naloxone. *Therapiewoche* **35**, 3943-3947 (1985).
48. Poulain, P.*, et al.* Efficacy and safety of transdermal buprenorphine: a randomized, placebo-controlled trial in 289 patients with severe cancer pain. *J Pain Symptom Manage* **36**, 117-125 (2008).
49. Ferrer-Brechner, T. & Ganz, P. Combination therapy with ibuprofen and methadone for chronic cancer pain. *Am J Med* **77**, 78-83 (1984).
50. Dellemijn, P.L., Verbiest, H.B., van Vliet, J.J., Roos, P.J. & Vecht, C.J. Medical therapy of malignant nerve pain. A randomised double-blind explanatory trial with naproxen versus slow-release morphine. *Eur J Cancer* **30a**, 1244-1250 (1994).
51. Moertel, C.G., Ahmann, D.L., Taylor, W.F. & Schwartau, N. Aspirin and pancreatic cancer pain. *Gastroenterology* **60**, 552-553 (1971).
52. van den Beuken-van Everdingen, M., Hochstenbach, L., Joosten, E., Tjan-Heijnen, V. & Janssen, D. Update on Prevalence of Pain in Patients With Cancer: Systematic Review and Meta-Analysis. *Journal of Pain and Symptom Management* **51**, 1070-1090.e1079 (2016).
53. Deandrea, S.*, et al.* Prevalence of breakthrough cancer pain: a systematic review and a pooled analysis of published literature. *J Pain Symptom Manage* **47**, 57-76 (2014).
54. Mercadante, S. & Bruera, E. Opioid switching: A systematic and critical review. *Cancer Treatment Reviews* **32**, 304-315 (2006).
55. Riley, J.*, et al.* Proposed 5-step World Health Organization analgesic and side effect ladder. *European Journal of Pain Supplements* **1**, 23-30 (2007).
56. Knudsen, J., Mortensen, S.M., Eikard, B. & Henriksen, H. [Morphine depot tablets compared with conventional morphine tablets in the treatment of cancer pain]. *Ugeskr Laeger* **147**, 780-784 (1985).
57. Thirlwell, M.P.*, et al.* Pharmacokinetics and clinical efficacy of oral morphine solution and controlled-release morphine tablets in cancer patients. *Cancer* **63**, 2275-2283 (1989).

58. Cundiff, D.*, et al.* Evaluation of a cancer pain model for the testing of long-acting analgesics. The effect of MS Contin in a double-blind, randomized crossover design. *Cancer* **63**, 2355-2359 (1989).
59. Ventafridda, V., Saita, L., Barletta, L., Sbanotto, A. & De Conno, F. Clinical observations on controlled-release morphine in cancer pain. *J Pain Symptom Manage* **4**, 124-129 (1989).
60. Hanks, G.W., Twycross, R.G. & Bliss, J.M. Controlled release morphine tablets: a double-blind trial in patients with advanced cancer. *Anaesthesia* **42**, 840-844 (1987).
61. Gourlay, G.K.*, et al.* Pharmacokinetics and pharmacodynamics of twenty-four-hourly Kapanol compared to twelve-hourly MS Contin in the treatment of severe cancer pain. *Pain* **69**, 295-302 (1997).
62. Gillette, J.*, et al.* Double-blind crossover clinical and pharmacokinetic comparison of oral morphine syrup and sustained release morphine sulfate capsules in patients with cancer-related pain. *Clinical Drug Investigation* **14**, 22-27 (1997).
63. Walsh, T. Clinical evaluation of slow release morphine tablets. *Advances in Pain Research and Therapy* **9**, 727-731 (1985).
64. Argoff, C.E. & Silvershein, D.I. A comparison of long- and short-acting opioids for the treatment of chronic noncancer pain: tailoring therapy to meet patient needs. *Mayo Clin Proc* **84**, 602-612 (2009).
65. Pederson, L. & Fredheim, O. Opioids for Chronic Noncancer Pain: Still No Evidence for Superiority of Sustained-Release Opioids. *Clinical Pharmacology and Therapeutics*, 97:114-115 (2014).
66. International Narcotics Control Board. *Report of the International Narcotics Control Board for 2016*, (INCB, 2016).
67. World Health Organization. *Cancer Pain Relief, 2nd Ed. With a guide to opioid availability.*, (WHO, Geneva, 1996).
68. Moulin, D.E., Kreeft, J.H., Murray-Parsons, N. & Bouquillon, A.I. Comparison of continuous subcutaneous and intravenous hydromorphone infusions for management of cancer pain. *Lancet; Feb 23 1991.* **337**, 465-468. (1991).
69. Bruera, E., Roca, E., Cedaro, L., Carraro, S. & Chacon, R. Action of oral methylprednisolone in terminal cancer patients: a prospective randomized double-blind study. *Cancer Treat Rep* **69**, 751-754 (1985).
70. Popiela, T., Lucchi, R. & Giongo, F. Methylprednisolone as palliative therapy for female terminal cancer patients. The Methylprednisolone Female Preterminal Cancer Study Group. *European journal of cancer & clinical oncology* **25**, 1823-1829 (1989).
71. Twycross, R.G. & Guppy, D. Prednisolone in terminal breast and bronchogenic cancer. *Practitioner* **229**, 57-59 (1985).
72. Della Cuna, G.R., Pellegrini, A. & Piazzi, M. Effect of methylprednisolone sodium succinate on quality of life in preterminal cancer patients: a placebo-controlled, multicenter study. The Methylprednisolone Preterminal Cancer Study Group. *Eur J Cancer Clin Oncol* **25**, 1817-1821 (1989).
73. Bruera, E.*, et al.* Dexamethasone in addition to metoclopramide for chronic nausea in patients with advanced cancer: a randomized controlled trial. *J Pain Symptom Manage* **28**, 381-388 (2004).
74. Yennurajalingam, S.*, et al.* Reduction of cancer-related fatigue with dexamethasone: a double-blind, randomized, placebo-controlled trial in patients with advanced cancer. *J Clin Oncol* **31**, 3076-3082 (2013).
75. Paulsen, O.*, et al.* Efficacy of methylprednisolone on pain, fatigue, and appetite loss in patients with advanced cancer using opioids: a randomized, placebo-controlled, double-blind trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **32**, 3221-3228 (2014).

76. Vyvey, M. Steroids as pain relief adjuvants. *Canadian Family Physician*, 56(12): 1295–1297. (2010).
77. Bruera, E. & Watanabe, S. Corticosteroids as adjuvant analgesics. *J Pain Symptom Manage*, 9(7):442-445. (1994).
78. International Medical Products Price Guide. Dexamethosone. (2015).
79. International Medical Products Price Guide. Prednisone. (2015).
80. International Medical Products Price Guide. Methylprednisolone. (2015).
81. Body, J.J*., et al.* Intravenous ibandronate reduces the incidence of skeletal complications in patients with breast cancer and bone metastases. *Ann Oncol* **14**, 1399-1405 (2003).
82. Body, J.J*., et al.* Oral ibandronate reduces the risk of skeletal complications in breast cancer patients with metastatic bone disease: results from two randomised, placebo-controlled phase III studies. *Br J Cancer* **90**, 1133-1137 (2004).
83. Broom, R.J*., et al.* Everolimus and zoledronic acid in patients with renal cell carcinoma with bone metastases: a randomized first-line phase II trial. *Clin Genitourin Cancer* **13**, 50-58 (2015).
84. Dearnaley, D.P*., et al.* A double-blind, placebo-controlled, randomized trial of oral sodium clodronate for metastatic prostate cancer (MRC PR05 Trial). *J Natl Cancer Inst* **95**, 1300-1311 (2003).
85. Diel, I*., et al.* Improved quality of life after long-term treatment with the bisphosphonate ibandronate in patients with metastatic bone disease due to breast cancer. *European journal of cancer (Oxford, England : 1990)* **40**, 1704-1712 (2004).
86. Elomaa, I*., et al.* Effect of oral clodronate on bone pain. A controlled study in patients with metastic prostatic cancer. *Int Urol Nephrol* **24**, 159-166 (1992).
87. Ernst, D.S*., et al.* A randomized, controlled trial of intravenous clodronate in patients with metastatic bone disease and pain. *J Pain Symptom Manage* **13**, 319-326 (1997).
88. Ernst, D.S*., et al.* A double-blind, crossover trial of intravenous clodronate in metastatic bone pain. *J Pain Symptom Manage* **7**, 4-11 (1992).
89. Ernst, D.S*., et al.* Randomized, double-blind, controlled trial of mitoxantrone/prednisone and clodronate versus mitoxantrone/prednisone and placebo in patients with hormone-refractory prostate cancer and pain. *J Clin Oncol* **21**, 3335-3342 (2003).
90. Heras, P., Kritikos, K., Hatzopoulos, A. & Georgopoulou, A.P. Efficacy of ibandronate for the treatment of skeletal events in patients with metastatic breast cancer. *Eur J Cancer Care (Engl)* **18**, 653-656 (2009).
91. Hortobagyi, G.N*., et al.* Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. Protocol 19 Aredia Breast Cancer Study Group. *N Engl J Med* **335**, 1785-1791 (1996).
92. James, N*., et al.* TRAPEZE: a randomised controlled trial of the clinical effectiveness and cost-effectiveness of chemotherapy with zoledronic acid, strontium-89, or both, in men with bony metastatic castration-refractory prostate cancer. *Health technology assessment (Winchester, England).* **20**, 1-288 (2016).
93. Kanis, J.A., Powles, T., Paterson, A.H., McCloskey, E.V. & Ashley, S. Clodronate decreases the frequency of skeletal metastases in women with breast cancer. *Bone* **19**, 663-667 (1996).
94. Kohno, N*., et al.* Zoledronic acid significantly reduces skeletal complications compared with placebo in Japanese women with bone metastases from breast cancer: a randomized, placebo-controlled trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **23**, 3314-3321 (2005).
95. Kristensen, B*., et al.* Oral clodronate in breast cancer patients with bone metastases: a randomized study. *J Intern Med* **246**, 67-74 (1999).
96. Kylmala, T*., et al.* Evaluation of the effect of oral clodronate on skeletal metastases with type 1 collagen metabolites. A controlled trial of the Finnish Prostate Cancer Group. *Eur J Cancer* **29A**, 821-825 (1993).

97. Lipton, A.*, et al.* Pamidronate prevents skeletal complications and is effective palliative treatment in women with breast carcinoma and osteolytic bone metastases: long term follow-up of two randomized, placebo-controlled trials. *Cancer* **88**, 1082-1090 (2000).
98. Martoni, A.*, et al.* Controlled clinical study on the use of dichloromethylene diphosphonate in patients with breast carcinoma metastasizing to the skeleton. *Oncology* **48**, 97-101 (1991).
99. Meulenbeld, H.*, et al.* Randomised phase II/III study of docetaxel with or without risedronate in patients with metastatic Castration Resistant Prostate Cancer (CRPC), the Netherlands Prostate Study (NePro). *European journal of cancer (Oxford, England : 1990)* **48**, 2993-3000 (2012).
100. Murakami, H.*, et al.* Phase II study of zoledronic acid combined with docetaxel for non-small-cell lung cancer: West Japan Oncology Group. *Cancer Sci* **105**, 989-995 (2014).
101. O'Rourke, N., McCloskey, E., Houghton, F., Huss, H. & Kanis, J.A. Double-blind, placebo-controlled, dose-response trial of oral clodronate in patients with bone metastases. *J Clin Oncol* **13**, 929-934 (1995).
102. Pan, Y.*, et al.* Docetaxel with or without zoledronic acid for castration-resistant prostate cancer. *International urology and nephrology* **46**, 2319-2326 (2014).
103. Paterson, A.H.*, et al.* Double-blind controlled trial of oral clodronate in patients with bone metastases from breast cancer. *J Clin Oncol* **11**, 59-65 (1993).
104. Piga, A.*, et al.* A double blind randomized study of oral clodronate in the treatment of bone metastases from tumors poorly responsive to chemotherapy. *J Exp Clin Cancer Res* **17**, 213-217 (1998).
105. Robertson, A.G., Reed, N.S. & Ralston, S.H. Effect of oral clodronate on metastatic bone pain: a double-blind, placebo-controlled study. *J Clin Oncol* **13**, 2427-2430 (1995).
106. Rosen, L.S.*, et al.* Zoledronic acid versus placebo in the treatment of skeletal metastases in patients with lung cancer and other solid tumors: a phase III, double-blind, randomized trial--the Zoledronic Acid Lung Cancer and Other Solid Tumors Study Group. *J Clin Oncol* **21**, 3150-3157 (2003).
107. Siris, E.S., Hyman, G.A. & Canfield, R.E. Effects of dichloromethylene diphosphonate in women with breast carcinoma metastatic to the skeleton. *Am J Med* **74**, 401-406 (1983).
108. Small, E.J., Smith, M.R., Seaman, J.J., Petrone, S. & Kowalski, M.O. Combined analysis of two multicenter, randomized, placebo-controlled studies of pamidronate disodium for the palliation of bone pain in men with metastatic prostate cancer. *J Clin Oncol* **21**, 4277-4284 (2003).
109. Smith, J., Jr. Palliation of painful bone metastases from prostate cancer using sodium etidronate: results of a randomized, prospective, double-blind, placebo-controlled study. *The Journal of urology* **141**, 85-87 (1989).
110. Smith, M.R.*, et al.* Randomized controlled trial of early zoledronic acid in men with castration-sensitive prostate cancer and bone metastases: results of CALGB 90202 (alliance). *J Clin Oncol* **32**, 1143-1150 (2014).
111. Theriault, R.L.*, et al.* Pamidronate reduces skeletal morbidity in women with advanced breast cancer and lytic bone lesions: a randomized, placebo-controlled trial. Protocol 18 Aredia Breast Cancer Study Group. *J Clin Oncol* **17**, 846-854 (1999).
112. Tripathy, D.*, et al.* Oral ibandronate for the treatment of metastatic bone disease in breast cancer: efficacy and safety results from a randomized, double-blind, placebo-controlled trial. *Ann Oncol* **15**, 743-750 (2004).
113. Tubiana-Hulin, M.*, et al.* [Double-blinded controlled study comparing clodronate versus placebo in patients with breast cancer bone metastases]. *Bull Cancer* **88**, 701-707 (2001).
114. Ueno, S.*, et al.* Efficacy of combined androgen blockade with zoledronic acid treatment in prostate cancer with bone metastasis: the ZABTON-PC (zoledronic acid/androgen blockade trial on prostate cancer) study. *Anticancer Res* **33**, 3837-3844 (2013).

115. van Holten-Verzantvoort, A.T.*, et al.* Reduced morbidity from skeletal metastases in breast cancer patients during long-term bisphosphonate (APD) treatment. *Lancet* **2**, 983-985 (1987).
116. van Holten-Verzantvoort, A.T.*, et al.* Palliative pamidronate treatment in patients with bone metastases from breast cancer. *J Clin Oncol* **11**, 491-498 (1993).
117. Vinholes, J., Purohit, O., Abbey, M., Eastell, R. & Coleman, R. Relationships between biochemical and symptomatic response in a double-blind randomised trial of pamidronate for metastatic bone disease. *Annals of oncology : official journal of the European Society for Medical Oncology* **8**, 1243-1250 (1997).
118. Wang, Y., Tao, H., Yu, X., Wang, Z. & Wang, M. Clinical significance of zoledronic acid and strontium-89 in patients with asymptomatic bone metastases from non-small-cell lung cancer. *Clin Lung Cancer* **14**, 254-260 (2013).
119. Zaghloul, M.S.*, et al.* A prospective, randomized, placebo-controlled trial of zoledronic acid in bony metastatic bladder cancer. *Int J Clin Oncol* **15**, 382-389 (2010).
120. Zarogoulidis, K.*, et al.* The impact of zoledronic acid therapy in survival of lung cancer patients with bone metastasis. *Int J Cancer* **125**, 1705-1709 (2009).
121. Theriault, R.*, et al.* Pamidronate reduces skeletal morbidity in women with advanced breast cancer and lytic bone lesions: a randomized, placebo-controlled trial. Protocol 18 Aredia Breast Cancer Study Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **17**, 846-854 (1999).
122. Rosen, L.*, et al.* Zoledronic acid versus placebo in the treatment of skeletal metastases in patients with lung cancer and other solid tumors: a phase III, double-blind, randomized trial--the Zoledronic Acid Lung Cancer and Other Solid Tumors Study Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **21**, 3150-3157 (2003).
123. Hortobagyi, G.*, et al.* Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. Protocol 19 Aredia Breast Cancer Study Group. *The New England journal of medicine* **18**, 1785-1791 (1996).
124. Body, J.*, et al.* Intravenous ibandronate reduces the incidence of skeletal complications in patients with breast cancer and bone metastases. *Annals of oncology : official journal of the European Society for Medical Oncology* **14**, 1399-1405 (2003).
125. Body, J.*, et al.* Oral ibandronate reduces the risk of skeletal complications in breast cancer patients with metastatic bone disease: results from two randomised, placebo-controlled phase III studies. *British journal of cancer* **90**, 1133-1137 (2004).
126. van Holten-Verzantvoort, A.*, et al.* Reduced morbidity from skeletal metastases in breast cancer patients during long-term bisphosphonate (APD) treatment. *Lancet* **2**, 983-985 (1987).
127. Rosen, L.*, et al.* Zoledronic acid is superior to pamidronate for the treatment of bone metastases in breast carcinoma patients with at least one osteolytic lesion. *Cancer* **100**, 36-43 (2004).
128. van Holten-Verzantvoort, A.*, et al.* Palliative pamidronate treatment in patients with bone metastases from breast cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **11**, 491-498 (1993).
129. Caraceni, A. & Portenoy, R.K. An international survey of cancer pain characteristics and syndromes. IASP Task Force on Cancer Pain. International Association for the Study of Pain. *Pain* **82**, 263-274 (1999).
130. Falk, S. & Dickenson, A.H. Pain and nociception: mechanisms of cancer-induced bone pain. *J Clin Oncol* **32**, 1647-1654 (2014).
131. Wong, R. & Wiffen, P.J. Bisphosphonates for the relief of pain secondary to bone metastases. *Cochrane Database Syst Rev*, CD002068 (2002).

132. Hoskin, P.*, et al.* A Multicenter Randomized Trial of Ibandronate Compared With Single-Dose Radiotherapy for Localized Metastatic Bone Pain in Prostate Cancer. *J Natl Cancer Inst* **107**, 107(110) pii: djv197. (2015).
133. Botteman, M.*, et al.* Cost effectiveness of bisphosphonates in the management of breast cancer patients with bone metastases. *Ann Oncol* **17**, 1072-1082 (2006).
134. Fleurence, R.L., Iglesias, C.P. & Johnson, J.M. The cost effectiveness of bisphosphonates for the prevention and treatment of osteoporosis: a structured review of the literature. *Pharmacoeconomics* **25**, 913-933 (2007).
135. Lippuner, K., Pollock, R., Smith-Palmer, J., Meury, T. & Valentine, W. A review of the cost effectiveness of bisphosphonates in the treatment of post-menopausal osteoporosis in Switzerland. *Appl Health Econ Health Policy*, 1;9(6):403-417. (2011).
136. Body, J., Lichinitser, M., Tjulandin, S., Garnero, P. & Bergstrom, B. Oral ibandronate is as active as intravenous zoledronic acid for reducing bone turnover markers in women with breast cancer and bone metastases. *Annals of oncology : official journal of the European Society for Medical Oncology* **18**, 1165-1171 (2007).
137. Choudhury, K.B.*, et al.* A randomized controlled trial to compare the efficacy of bisphosphonates in the management of painful bone metastasis. *Indian J Palliat Care* **17**, 210-218 (2011).
138. Wang, F.*, et al.* Comparison between zoledronic acid and clodronate in the treatment of prostate cancer patients with bone metastases. *Medical oncology (Northwood, London, England)* **30**, 657 (2013).
139. Grond, S., Zech, D., Diefenbach, C., Radbruch, L. & Lehmann, K.A. Assessment of cancer pain: a prospective evaluation in 2266 cancer patients referred to a pain service. *Pain* **64**, 107-114 (1996).
140. Toussaint, N.D., Elder, G.J. & Kerr, P.G. Bisphosphonates in chronic kidney disease; balancing potential benefits and adverse effects on bone and soft tissue. *Clin J Am Soc Nephrol* **4**, 221-233 (2009).
141. Sopata, M.*, et al.* Efficacy and safety of tanezumab in the treatment of pain from bone metastases. *Pain* **156**, 1703-1713 (2015).
142. Lipton, A.*, et al.* Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: a combined analysis of 3 pivotal, randomised, phase 3 trials. *Eur J Cancer* **48**, 3082-3092 (2012).
143. Body, J.J.*, et al.* A study of the biological receptor activator of nuclear factor-kappaB ligand inhibitor, denosumab, in patients with multiple myeloma or bone metastases from breast cancer. *Clin Cancer Res* **12**, 1221-1228 (2006).
144. Lipton, A.*, et al.* Extended efficacy and safety of denosumab in breast cancer patients with bone metastases not receiving prior bisphosphonate therapy. *Clinical cancer research : an official journal of the American Association for Cancer Research* **14**, 6690-6696 (2008).
145. Fizazi, K.*, et al.* Randomized phase II trial of denosumab in patients with bone metastases from prostate cancer, breast cancer, or other neoplasms after intravenous bisphosphonates. *J Clin Oncol* **27**, 1564-1571 (2009).
146. Stopeck, A.T.*, et al.* Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. *J Clin Oncol* **28**, 5132-5139 (2010).
147. Henry, D.H.*, et al.* Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. *J Clin Oncol* **29**, 1125-1132 (2011).
148. Fizazi, K.*, et al.* Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. *Lancet* **377**, 813-822 (2011).

149. Martin, M.*, et al.* Bone-related complications and quality of life in advanced breast cancer: results from a randomized phase III trial of denosumab versus zoledronic acid. *Clin Cancer Res* **18**, 4841-4849 (2012).
150. Cleeland, C.S.*, et al.* Pain outcomes in patients with advanced breast cancer and bone metastases: results from a randomized, double-blind study of denosumab and zoledronic acid. *Cancer* **119**, 832-838 (2013).
151. Green, W. Denosumab (Prolia) Injection. A New Approach to the Treatment of Women With Postmenopausal Osteoporosis. . *Pharmacy and Therapeutics*, 35(10): 553–559. (2010).
152. Fallon, M.T. Neuropathic pain in cancer. *Br J Anaesth* **111**, 105-111 (2013).
153. Mishra, S., Bhatnagar, S., Goyal, G.N., Rana, S.P. & Upadhya, S.P. A comparative efficacy of amitriptyline, gabapentin, and pregabalin in neuropathic cancer pain: a prospective randomized double-blind placebo-controlled study. *Am J Hosp Palliat Care* **29**, 177-182 (2012).
154. Sjolund, K.F., Yang, R., Lee, K.H. & Resnick, M. Randomized study of pregabalin in patients with cancer-induced bone pain. *Pain Ther* **2**, 37-48 (2013).
155. Dou, Z., Jiang, Z. & Zhong, J. Efficacy and safety of pregabalin in patients with neuropathic cancer pain undergoing morphine therapy. *Asia Pac J Clin Oncol* **13**, e57-e64 (2017).
156. Chen, D.L., Li, Y.H., Wang, Z.J. & Zhu, Y.K. The research on long-term clinical effects and patients' satisfaction of gabapentin combined with oxycontin in treatment of severe cancer pain. *Medicine (Baltimore)* **95**, e5144 (2016).
157. World Health Organization. The Selection and Use of Essential Medicines: WHO Technical Report Series - 1006. Report of the WHO Expert Committee, 2017 (including the 20th WHO Model List of Essential Medicines and the 6th Model List of Essential Medicines for Children. (2017).
158. United States ex rel. Franklin v. Parke-Davis. in *U.S. District Court for the Distric of Massachusetts,* (D. Mass. 2001, 1995).
159. U.S. Department of Justice. Warner-Lambert to pay $430 million to resolve criminal & civil. (2004).
160. Steinman, M.A., Bero, L.A., Chren, M.M. & Landefeld, C.S. Narrative review: the promotion of gabapentin: an analysis of internal industry documents. *Ann Intern Med* **145**, 284-293 (2006).
161. Saris, P. Findings of fact and conclusions of law. In re Neurontin. in *Civil Action No. 04-cv-10739-PBS, 2010 WL 4325225.* (United States Department of Justice., 2010).
162. Vedula, S.S., Bero, L., Scherer, R.W. & Dickersin, K. Outcome reporting in industry-sponsored trials of gabapentin for off-label use. *New England Journal of Medicine*, 361(320):1963–1971. (2009).
163. Vedula, S.S., Goldman, P.S., Rona, I.J., Greene, T.M. & Dickersin, K. Implementation of a publication strategy in the context of reporting biases. A case study based on new documents from Neurontin litigation. *Trials* **13**, 136 (2012).
164. Vedula, S.S., Li, T. & Dickersin, K. Differences in reporting of analyses in internal company documents versus published trial reports: comparisons in industry-sponsored trials in off-label uses of gabapentin. *PLoS Med* **10**, e1001378 (2013).
165. Dickersin, K. Reporting and other biases in studies of Neurontin for migraine, psychiatric/bipolar disorders, nociceptive pain, and neuropathic pain. in *Researchgate* (2008).
166. Altundağ, M.B., Üçer, A.R., Çalikoğlu, T. & Güran, Z. Single (500 cGy, 800 cGy) and multifraction (300x10 cGy) radiotherapy schedules in the treatment of painful bone metastases. *THOD Turk Hematol.-Onkol. Derg.* **12**, 16-21 (2002).
167. Amouzegar-Hashemi, F., Behrouzi, H., Kazemian, A., Zarpak, B. & Haddad, P. Single versus multiple fractions of palliative radiotherapy for bone metastases: a randomized clinical trial in Iranian patients. *Curr Oncol.* **15**, 151. (2008).

168. Anter, A.H. Single Fraction versus Multiple Fraction Radiotherapy for treatment of painful bone metastases: A Prospective Study; Mansoura experience. *Forum of Clinical Oncology* **6**, 8-13 (2015).
169. Badzio, A.*, et al.* 20 Gy in five fractions versus 8 Gy in one fraction in palliative radiotherapy of bone metastases. A multicenter randomized study. **53**, 261-264 (2003).
170. Bone Pain Trial Working, P. 8 Gy single fraction radiotherapy for the treatment of metastatic skeletal pain: randomised comparison with a multifraction schedule over 12 months of patient follow-up. *Radiother Oncol* **52**, 111-121 (1999).
171. Chow, E.*, et al.* Single versus multiple fractions of repeat radiation for painful bone metastases: a randomised, controlled, non-inferiority trial. *Lancet Oncol* **15**, 164-171 (2013).
172. Foro Arnalot, P.*, et al.* Randomized clinical trial with two palliative radiotherapy regimens in painful bone metastases: 30 Gy in 10 fractions compared with 8 Gy in single fraction. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology* **89**, 150-155 (2008).
173. Gaze, M.N.*, et al.* Pain relief and quality of life following radiotherapy for bone metastases: a randomised trial of two fractionation schedules. *Radiother Oncol.* **45**, 109-116. (1997).
174. Gutierrez Bayard, L., Salas Buzon Mdel, C., Angulo Pain, E. & de Ingunza Baron, L. Radiation therapy for the management of painful bone metastases: Results from a randomized trial. *Reports of practical oncology and radiotherapy : journal of Greatpoland Cancer Center in Poznan and Polish Society of Radiation Oncology* **19**, 405-411 (2014).
175. Hamouda, W.E., Roshdy, W. & Teema, M. Single versus conventional fractionated radiotherapy in the palliation of painful bone metastases. *Gulf J Oncolog.* **1**, 35-41. (2007).
176. Hartsell, W.F.*, et al.* Randomized trial of short- versus long-course radiotherapy for palliation of painful bone metastases. *Journal of the National Cancer Institute* **97**, 798-804 (2005).
177. Kagei, K.*, et al.* [A randomized trial of single and multifraction radiation therapy for bone metastasis: a preliminary report]. *Gan No Rinsho.* **36**, 2553-2558. (1990).
178. Koswig, S. & Budach, V. Remineralisation und Schmerzlinderung von Knochenmetastasen nach unterschiedlich fraktionierter Strahlentherapie (10mal 3 Gy vs. 1mal 8 Gy) Eine prospektive Studie. *Strahlentherapie und Onkologie* **175**, 500-508 (1999).
179. Nielsen, O.S., Bentzen, S.M., Sandberg, E., Gadeberg, C.C. & Timothy, A.R. Randomized trial of single dose versus fractionated palliative radiotherapy of bone metastases. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology* **47**, 233-240 (1998).
180. Price, P.*, et al.* Prospective randomised trial of single and multifraction radiotherapy schedules in the treatment of painful bony metastases. *Radiother Oncol.* **6**, 247-255. (1986).
181. Roos, D.E.*, et al.* Randomized trial of 8 Gy in 1 versus 20 Gy in 5 fractions of radiotherapy for neuropathic pain due to bone metastases (Trans-Tasman Radiation Oncology Group, TROG 96.05). *Radiother Oncol* **75**, 54-63 (2005).
182. Sarkar, S.K., Sarkar, S., Pahari, B. & Majumdar, D. Multiple and single fraction palliative radiotherapy in bone secondaries - A prospective study. **12**, 281-284 (2002).
183. van der Linden, Y.M.*, et al.* Single fraction radiotherapy is efficacious: a further analysis of the Dutch Bone Metastasis Study controlling for the influence of retreatment. *Int J Radiat Oncol Biol Phys.* **59**, 528-537. doi: 510.1016/j.ijrobp.2003.1010.1006. (2004).
184. Cole, D.J. A randomized trial of a single treatment versus conventional fractionation in the palliative radiotherapy of painful bone metastases. *Clinical oncology (Royal College of Radiologists (Great Britain))* **1**, 59-62 (1989).
185. Foro, P., Algara, M., Reig, A., Lacruz, M. & Valls, A. Randomized prospective trial comparing three schedules of palliative radiotherapy. Preliminary results. *Oncologia (Spain)* **21**, 55-60 (1998).
186. Meeuse, J.J.*, et al.* Efficacy of radiotherapy for painful bone metastases during the last 12 weeks of life: results from the Dutch Bone Metastasis Study. *Cancer* **116**, 2716-2725 (2010).

187. Özsaran, Z., Yalman, D., Anacak, Y., Esassolak, M. & Haydaroğlu, A. Palliative radiotherapy in bone metastases: Results of a randomized trial comparing three fractionation schedules. **6**, 43-48 (2001).
188. Safwat, E., El-Nahas, T., Metwally, H., Abdelmotgally, R. & Kassem, N. Palliative fractionated radiotherapy for bone metastases clinical and biological assessment of single versus multiple fractions. *J Egypt Natl Canc Inst.* **19**, 21-27. (2007).
189. Steenland, E.*, et al.* The effect of a single fraction compared to multiple fractions on painful bone metastases: a global analysis of the Dutch Bone Metastasis Study. *Radiother Oncol.* **52**, 101-109. (1999).
190. Dennis, K., Makhani, L., Zeng, L., Lam, H. & Chow, E. Single fraction conventional external beam radiation therapy for bone metastases: a systematic review of randomised controlled trials. *Radiother Oncol* **106**, 5-14 (2013).
191. Chow, E.*, et al.* Update on the systematic review of palliative radiotherapy trials for bone metastases. *Clin Oncol (R Coll Radiol)* **24**, 112-124 (2012).
192. Yoon, F. & Morton, G.C. Single fraction radiotherapy versus multiple fraction radiotherapy for bone metastases in prostate cancer patients: comparative effectiveness. *Cancer Manag Res* **6**, 451-457 (2014).
193. Storto, G.*, et al.* Impact of (1)(8)F-fluoride PET-CT on implementing early treatment of painful bone metastases with Sm-153 EDTMP. *Nuclear medicine and biology* **40**, 518-523 (2013).
194. Parker, C.*, et al.* Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med* **369**, 213-223 (2013).
195. James, N.*, et al.* TRAPEZE: a randomised controlled trial of the clinical effectiveness and cost-effectiveness of chemotherapy with zoledronic acid, strontium-89, or both, in men with bony metastatic castration-refractory prostate cancer. *Health technology assessment (Winchester, England)* **20**, 1-288 (2016).
196. Buchali, K.*, et al.* Results of a double blind study of 89-strontium therapy of skeletal metastases of prostatic carcinoma. *Eur J Nucl Med* **14**, 349-351. (1988).
197. Han, S.H.*, et al.* The PLACORHEN study: a double-blind, placebo-controlled, randomized radionuclide study with (186)Re-etidronate in hormone-resistant prostate cancer patients with painful bone metastases. Placebo Controlled Rhenium Study. *J Nucl Med.* **43**, 1150-1156. (2002).
198. Porter, A.T. & McEwan, A.J. Strontium-89 as an adjuvant to external beam radiation improves pain relief and delays disease progression in advanced prostate cancer: results of a randomized controlled trial. *Semin Oncol.* **20**, 38-43. (1993).
199. Sartor, O.*, et al.* Samarium-153-Lexidronam complex for treatment of painful bone metastases in hormone-refractory prostate cancer. *Urology.* **63**, 940-945. doi: 910.1016/j.urology.2004.1001.1034. (2004).
200. Maxon, H.R., 3rd*, et al.* Rhenium-186(Sn)HEDP for treatment of painful osseous metastases: results of a double-blind crossover comparison with placebo. *J Nucl Med.* **32**, 1877-1881. (1991).
201. Serafini, A.N.*, et al.* Palliation of pain associated with metastatic bone cancer using samarium-153 lexidronam: a double-blind placebo-controlled clinical trial. *J Clin Oncol.* **16**, 1574-1581. doi: 1510.1200/JCO.1998.1516.1574.1574. (1998).